VOLUME 36 DECEMBER 17, 1971 NUMBER 25 JOCEAH

THE JOURNAL OF Organic Chemistry

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ACADEMIC PRESS NEW YORK AND LONDON
111 FIFTH AVENUE, NEW YORK, N.Y. 10003

THE JOURNAL OF Organic Chemistry

Published biweekly by the American Chemical Society at 20th and Northampton Streets, Easton, Pennsylvania

Published biweekly by the American Chemical Society at 20th and Northampton Sts., Easton, Pa. 18042. Second-class postage paid at Washington, D. C., and at additional mailing offices.

Production Staff: Manager, Editorial Production, CHARLES R. BERTSCH; Production Editor, EILEEN SEGAL; Assistant Editor, FERN S. JACKSON; Editorial Assistant, DEBORAH K. MILLER

Advertising Office: Century Communication Corporation, 142 East Ave., Norwalk, Conn. 06851.

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THE JOURNAL OF Organic Chemistry®

VOLUME 36, NUMBER 25

DECEMBER 17, 1971

Hybridization on Amine Nitrogens and pK_a Values of Some *N*-(4-Nitrophenyl)polymethylenimines

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Received March 11, 1971

The ultraviolet and nmr spectra and the ionization constants of a series of *N*-(4-nitrophenyl)polymethylenimines, 4-$NO_2C_6H_4N$-$(CH_2)_n$, with n = 2–6, have been determined. The uv and nmr spectra indicate that where n = 2 the amine nitrogen is near-sp^3 hybridized, and where n = 3–6 hybridization is near-sp^2. Comparison of the pK_a values for the above series with those for *N*-(4-carboxyphenyl)-, *N*-phenyl-, and *N*-methylpolymethylenimines allows a rough estimate of the magnitude of the effect of differing hybridization on pK_a's. This effect leads to base strengthening by *ca.* 2.3 pK units, in the case of *N*-(4-nitrophenyl)aziridine, and is believed to account for about 1.0–1.5 of the 3.7–4.2 unit difference between pK_a's of corresponding aniline and 4-nitroaniline derivatives.

Relative basicities of substituted aniline, *N*,*N*-dialkylaniline, and *N*-phenylpolymethyleneimine derivatives are controlled by a variety of factors which often interact in complex manners. These include inductive and mesomeric effects of N and ring substitutents;[1-3] differing solvation stabilization of the free bases,[4,5] or the conjugate anilinium ions;[1,6] steric effects, which might involve changes in the dihedral angle between the lone pair of the amine group and the plane of the ring as a consequence of alkyl-ortho repulsions,[7] as well as increases or decreases in bond-opposition strain on protonation;[8] relief of bond-angle strain on protonation;[8] and, finally, differences in hybridization on the amine nitrogens,[5,9] which influence the amount of orbital overlap and hence the extent of lone-pair charge-delocalization to the ring. Although relatively little attention has been devoted to the latter factor in the extensive literature relating to aromatic amine basicities, the results of some recent studies suggest that hybridization should play an important part in differences between pK_a values of corresponding aniline and nitroaniline derivatives.

Earlier widely held misconceptions[10,11] that the amine nitrogens in aniline and its *N*,*N*-dialkyl derivatives might be sp^2 hybridized have recently been resolved. Bottini and Nash[12] have shown from pK_a and uv spectral investigations and several other groups of workers[13,14] have shown from molecular polarizability studies that the configurations about nitrogen in these amines are more or less pyramidal (*i.e.*, near-sp^3 hybridized in aniline in nonhydroxylic solvents, slightly flattened pyramidal in *N*,*N*-dimethylaniline).[13,15]

The substituents about the amine nitrogens in 4-nitroaniline and its *N*,*N*-dimethyl derivative, on the other hand, are essentially coplanar (*i.e.*, sp^2) in the solid phase or nonhydroxylic solvents as shown by total crystal structure[16] and molecular polarizability determinations.[17] Studies on *p*-carboxyphenylpolymethylenimine ionization constants and *p*-nitrophenylpolymethylenimine reduction rates[9] provide evidence that the same also applies for most $-M$ 4-substituted aniline derivatives in hydroxylic solvents.

A logical consequence of these findings would be that pK_a

(1) E. Folkers and O. Runquist, *J. Org. Chem.*, **29**, 830 (1964).
(2) M. M. Fiekling, A. Fischer, B. R. Mann, J. Packer, and J. Vaughan, *J. Amer. Chem. Soc.*, **81**, 4226 (1959).
(3) A. I. Biggs and R. A. Robinson, *J. Chem. Soc.*, 388 (1961).
(4) C. P. Nash and G. E. Maciel, *J. Phys. Chem.*, **68**, 831 (1964).
(5) J. W. Eastes, M. H. Aldridge, and M. J. Kamlet, *J. Chem. Soc. B*, 922 (1969).
(6) H. K. Hall, Jr., *J. Amer. Chem. Soc.*, **79**, 5441 (1957).
(7) B. M. Wepster in "Progress in Stereochemistry," W. Klyne and P. B. de la Mere, Ed., Vol. II, Butterworths, London, 1958, Chapter 4.
(8) H. C. Brown, R. S. Fletcher, and R. B. Johannesen, *J. Amer. Chem. Soc.*, **73**, 212 (1951); E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill, New York, N. Y., 1962, Section 9-4.
(9) W. D. Weringa and M. J. Janssen, *Recl. Trav. Chim. Pays-Bas*, **87**, 1372 (1968).
(10) H. T. Taylor, *Nature*, **181**, 265 (1958).
(11) H. C. Brown and A. Cahn, *J. Amer. Chem. Soc.*, **72**, 2939 (1950).
(12) A. Bottini and C. P. Nash, *ibid.*, **84**, 734 (1962).
(13) M. J. Aroney, R. J. W. Le Fevre, L. Radom, and G. L. D. Ritchie, *J. Chem. Soc. B*, 507 (1968).
(14) C. W. N. Cumper and A. Singleton, *ibid.*, 645 (1968).
(15) The effect of hydrogen bonding should be toward nearer sp^3 hybridization in hydroxylic solvents (see following paper).
(16) T. C. W. Mak and J. Trotter, *Acta Crystallogr.*, **18**, 68 (1965).
(17) M. J. Aroney, K. E. Calderbank, R. J. W. Le Fevre, and R. K. Pierens, *J. Chem. Soc. B*, 561 (1968).

or reactivity changes in going through a Hammett series from positively to negatively 4-substituted aniline derivatives should incorporate important terms attributable to the changing amine nitrogen hybridization. This serves as the basis for some interesting conjecture regarding the many ρ–σ relationships which have been reported for such compounds, since changing conformations about amine nitrogen have never been considered in the standard linear free energy treatments.

The present investigation represents an attempt to unravel the various factors influencing basicities and reactivities of aromatic amines and to assess the magnitudes of effects of changing hybridization. Toward these ends, we have determined the ionization constants as well as the uv and nmr spectra of the *N*-(4-nitrophenyl)polymethylenimines, $4\text{-}NO_2C_6H_4N\text{-}(CH_2)_n$, with n = 2–6. It was anticipated that in this series hybridization on amine nitrogens would change with ring size, with other effects hopefully following established patterns. The reasoning governing our approach toward untangling the interacting factors mentioned in our introductory remarks was that pK_a's would reflect electronic, steric, and solvation effects on both sides of the ionization equilibria, while the spectra should reflect only effects in the free bases.

Results

Ultraviolet and Nmr Spectra.—Listed in Table I, together with comparison results for *N*,*N*-dimethyl- (**1**) and *N*,*N*-diethyl-4-nitroaniline (**2**), are uv spectral data in water for the [$^+R_2N{=}C(1) \rightarrow C(4){=}NO_2^-$] bands and nmr line positions in acetone-d_6 for the 2,6 protons of *N*-(4-nitrophenyl)aziridine (**3**), -azetidine (**4**), -pyrrolidine (**5**), -piperidine (**6**) and -hexamethylenimine (**7**).

TABLE I
ULTRAVIOLET AND NMR SPECTRAL DATA FOR SOME *N*-(4-NITROPHENYL)POLYMETHYLENIMINES

Compd	4-$NO_2C_6H_4R$, R =	$\lambda_{max}^{H_2O}$, nm	$\epsilon \times 10^{-3}$	δ^a
1	$(CH_3)_2N$–	420	19.9	6.72
2	$(C_2H_5)_2N$–	430	22.9	6.74
3	$(CH_2)_2$–N–	325	10.8	7.12
4	$(CH_2)_3$–N–	422	17.4	6.32
5	$(CH_2)_4$–N–	433	23.5	6.57
6	$(CH_2)_5$–N–	425	16.1	6.92
7	$(CH_2)_6$–N–	430	22.9	6.72

[a] Chemical shifts in parts per million for the 2,6 protons in acetone-d_6; midpoints of doublets, $J_{BH} \sim 0.10$ ppm; TMS internal standard; determined on Varian HA-100 nmr spectrometer.

From these results, our initial expectation that the three- and four-membered ring compounds would show appreciably more p character in amine nitrogen hybridization appears to have been borne out only in the case of the *N*-(4-nitrophenyl)aziridine (**3**). A 100-nm blue shift for the [$^+R_2N{=}C(1) \rightarrow C(4){=}NO_2^-$] electronic transition of **3** relative to the other compounds studied[18] implies significantly decreased delocalization of the amine lone-pair electrons to the ring, as would be expected with near-sp^3 hybridization. Markedly enhanced deshielding of the 2 and 6 protons in the nmr[19] (shifted downfield by about 0.4 ppm relative to **1** or **2**) is also consistent with appreciably lessened amine → ring resonance interaction.[20]

With *N*-(4-nitrophenyl)azetidine (**4**), on the other hand, indications of strong "through conjugation," implying near-sp^2 hybridization on the amine nitrogen, were obtained from the uv spectrum, which closely resembled those of the other nitroaniline derivatives studied, and from the chemical shift of the 2,6 protons, which was found further *upfield* than corresponding signals in all the other amines.[19] We regard a planar conformation about nitrogen in a four-membered ring compound as one of the more surprising findings of this investigation and as a good indicator of relative contributions of ring strain and mesomerism to overall free energies in the arylpolymethylenimines.

The sharply decreased ϵ_{max} value for *N*-(4-nitrophenyl)-piperidine (**6**) with only minor dispacement in λ_{max} relative to the pyrrolidine (**5**) or the hexamethylenimine (**7**) deserves comment. Such an effect is characteristic of classical steric inhibition of resonance and is readily rationalized as resulting from a twisting of the piperidine group from the ring plane as a consequence of alkyl-ortho repulsions, which would be greater in **6** than in **5** or **7** because of the relative rigidity of the chair form of the six-membered ring.[21] Decreased amine → ring mesomerism, resulting from such a steric inhibition of resonance effect, is also consistent with the 0.2–0.3-ppm downfield shift for the 2,6-proton signal in **6** relative to **1**, **2**, **5**, and **7**,[23] as well as the markedly enhanced rate of disodium disulfide reduction of **6** compared with **1**, **2**, and **5** in aqueous methanol as reported by Weringa and Janssen.[9]

The latter authors[9] have also provided confirmatory information regarding electronic and steric effects in closely related free bases with the following pK_a values for 4-dialkylaminobenzoic acids in 50% ethanol:[24] Me_2N–, 6.01; Et_2N–, 6.19; pyrrolidino, 6.07; piperidino, 5.75. The decreased pK_a for the piperidine compound is, as above, attributed to decreased mesomerism resulting from twisting of the amine plane from the ring plane.[25]

(18) That λ_{max} values shifted increasingly to the red with increasing polarity in a series of nonhydroxylic solvents, and that shifts were proportional for all compounds (see following paper) implies that we are dealing with corresponding electronic transitions.

(19) Effects are similar, but of smaller magnitudes, for 3,5-proton signals.

(20) I. D. Rae, *Aust. J. Chem.*, **18**, 1807 (1965); **20**, 2381 (1967).

(21) The angle of twist, θ, is calculated to be 33° in **6** from the $\cos^2\theta = \epsilon/\epsilon_0$ relationship[22] (on the assumption that ϵ_0, is the average of the ϵ_{max} values for **5** and **7**). Unsubstituted *N*-phenylpiperidine also shows sharply diminished absorption intensity relative to the corresponding pyrrolidine, probably for analogous reasons.[12] Here the angle of twist (in methanol) is calculated to be about 45°.

(22) E. A. Braude and F. Sondheimer, *J. Chem. Soc.*, 3754 (1955); H. H. Jaffé and M. Orchin, "Theory and Applications of Ultraviolet Spectroscopy," Wiley, New York, N. Y., 1962, Section 15.3.

(23) For comparison with a more frequently cited example of steric inhibition of resonance, the 6-proton signal of *N*,*N*,2-trimethyl-4-nitroaniline is also shifted downfield by about 0.2 ppm relative to the 2,6-proton signal of **1**.

(24) We are dealing here with the $-COOH \rightleftarrows -COO^-$ equilibrium for these compounds. We will have occasion later to discuss pK_a's in the amine protonation equilibrium.

(25) It is a constructive exercise to assume the angle of twist, θ, in 4-piperidinobenzoic acid to be intermediate between that for **6** and *N*-phenylpiperidine,[21] *i.e.*, *ca.* 36–39°, and apply Taft's treatment, $\sigma_R/\sigma_R^0 = \epsilon/\epsilon_0 = \cos^2\theta$ [R. W. Taft and H. D. Evans, *J. Chem. Phys.*, **27**, 1427 (1957)]. If we take for σ_R^0 the value for the Me_2N– group, −0.83, the $\Delta\sigma_R$ term due to twisting from planarity becomes +0.29 to +0.33. With a ρ value near 1.0, the decrease in the pK_a for the 4-piperidino relative to the other benzoic acid derivatives is hence also quantitatively accountable for by a straightforward steric inhibition of resonance effect.

TABLE II

DISSOCIATION CONSTANTS OF SOME POLYMETHYLENIMINE DERIVATIVES

R	4-$NO_2C_6H_4R$		4-$HOOCC_6H_4R$		C_6H_5R		CH_3R	
	pK_a[a]	ΔpK_a[b]	pK_a[c]	ΔpK_a[b]	pK_a[d]	ΔpK_a[b]	pK_a[e]	ΔpK_a[b]
$(CH_3)_2N-$	0.65		1.40		4.22[f] 4.39[g]		9.76	
$(CH_3CH_2)_2N-$	1.75	+1.1	2.45	+1.1	5.71[f] 5.85[g] 5.59[h]	+1.5[i]	10.29	+0.5
$(CH_2)_2$–N–	0.9–1.2[i]	+0.4					7.86	−1.9
$(CH_2)_3$–N–	0.34	−0.3			4.08[g]	−0.3[i]	10.40	+0.6
$(CH_2)_4$–N–	−0.42	−1.1	0.39	−1.0	3.71[f] 3.45[g] 3.24[h]	−0.7[i]	10.46	+0.7
$(CH_2)_5$–N–	2.46	+1.8	2.67	+1.3	4.60[f] 5.22[g] 4.93[h]	+0.7[i]	10.08	+0.3
$(CH_2)_6$–N–	−0.15	−0.8						

[a] Present investigation, H_2O, 25°. [b] Relative to *N*,*N*-dimethyl derivative. [c] Reference 9, 50% EtOH, 25°. [d] 50% EtOH. [e] Reference 27, H_2O, 25°. [f] Reference 30, 20°. [g] References 4 and 12, 25°. [h] Reference 9, 25°. [i] See Experimental Section regarding uncertainties in determination. [j] Best estimates by comparison of results from corresponding references.

Taken together, the results cited above allow no unequivocal choice of order of amine → ring electron donation among **1**, **2**, **4**, **5**, and **7**; indeed the order may be solvent dependent. However, diminished mesomerism in the aziridine derivative **3** because of more p character in the hybridization on nitrogen and in the piperidine derivative **6** because of alkyl-ortho repulsions seems reasonably well established.

Dissociation Constants.—The pK_a values for **1**–**7** in water at 25.0 ± 0.1° are listed in Table II, together with comparison literature data for some corresponding *N*-(4-carboxyphenyl)-, *N*-phenyl-, and *N*-methylpolymethylenimines. As is seen, the pK_a's for the sp^2-hybridized 4-nitroaniline derivatives vary over a 2.9 pK unit range from −0.42 to +2.46, and the 0.9–1.2 value for the sp^3-hybridized aziridinyl derivative **3** falls near the average for all compounds studied.[26] Assessment of a ΔpK_a term, attributable to the difference in hybridization, is therefore impossible from the raw data, and it becomes necessary to eliminate or evaluate some important obtruding effects.

Toward this end, we have also listed ΔpK_a values in Table II, representing differences in pK_a between the polymethylenimine and corresponding dimethylamine derivatives in each series. In the case of the alkylpolymethylenimines (last column), these ΔpK_a's are considered to be measures of combined solvation, inductive, ring-side, and bond-opposition effects on relative amine basicities where no changes in hybridization occur on protonation.[27]

These same effects are believed to be reflected in the three arylpolymethylenimine series, but in addition the ΔpK_a's are here considered to show the effects of differences in amine → ring mesomerism between planar and pyramidally hybridized free bases, as well as I-strain differences between the free bases and their salts caused by possible changes in hybridization on protonation.

The $\Delta\Delta pK_a$ values which are listed in Table III

TABLE III

$\Delta\Delta pK_a$ VALUES FOR *N*-ARYLPOLYMETHYLENIMINES

R	NO_2-C_6H_4R	HOOC-C_6H_4R	Registry no.	C_6H_5R	Registry no.
$(C_2H_5)_2N-$	+0.6	+0.6	5429-28-7	+1.0	91-66-7
$(CH_2)_2$–N–	+2.3				
$(CH_2)_3$–N–	−0.9			−0.9	3334-89-2
$(CH_2)_4$–N–	−1.8	−1.7	22090-27-3	−1.4	4096-21-3
$(CH_2)_5$–N–	+1.5	+1.0	22090-24-0	+0.4	4096-20-2

represent differences between ΔpK_a's in the aryl- and the methylpolymethylenimine series, with the common effects presumably cancelling one another out. Hence, they are considered to be rough measures of basicity changes attributable to hybridization effects, either those deriving from differing hybridization in the free bases, or those arising from changing hybridization on protonation. The approximations involved in arriving at these $\Delta\Delta pK_a$'s preclude quantitative intercomparisons, but they do reflect some of the trends which would be anticipated from *a priori* considerations.

Discussion

Effects on Basicity Attributable to Changing Hybridization.—The base-weakening effect (negative $\Delta\Delta pK_a$) for the nitrophenylpyrrolidine **5** (and probably for the hexamethylenimine **7**, if comparison data for *N*-methylhexamethylenimine were available) and the base-strengthening effect (positive $\Delta\Delta pK_a$) for the nitrophenylpiperidine **6**, are fully consistent with Brown's generalizations regarding I strain.[8] The protonation reactions in these instances are sp^2 → sp^3 transformations; I-strain theory predicts that incursions of bond-opposition strain should lead to sp^2 → sp^3 transformations being more difficult for five- and seven-membered ring compounds, while relief of bond-opposition strain should make such transformations more facile for six-membered rings. The negative $\Delta\Delta pK_a$ (base weakening) for *N*-(4-nitrophenyl)azetidine confirms the conclusion regarding sp^2 hybridization in the free base and implies that strong bond-

(26) A rapid acid-catalyzed ring-opening reaction leads to difficulties in measuring the pK_a of **3**. See Experimental Section for information regarding precision of the measurement.

(27) S. Searles, M. Tamres, F. Block, and L. A. Quarterman, *J. Amer. Chem. Soc.*, **78**, 4917 (1956). Particularly to be noted is the −1.9 unit ΔpK_a value for *N*-methylaziridine relative to trimethylamine.

eclipsing strains more than offset effects of the *ca.* 10° relief of bond-angle strain in going to the sp^3 anilinium ion.

The base strengthening in the case of **6** derives from two causes: the I-strain effect noted here and the steric inhibition of resonance effect in the free base noted earlier. The progression of $\Delta\Delta pK_a$ values in Table III from near-sp^3-hybridized *N*-phenylpiperidine to near-sp^2-hybridized *N*-(4-carboxyphenyl)piperidine and **6** suggests that relief of bond-opposition strain is the greater contributer to the observed result.[28]

We have no unequivocal explanation for the negative $\Delta\Delta pK_a$ values for *N*-phenylazetidine and *N*-phenylpyrrolidine.[29] It may be that these have somewhat "flattened pyramidal" configurations about nitrogen (*i.e.*, intermediate hybridization), and that the same considerations apply as with **4** and **5**. Alternatively, some as yet unrecognized effect, possibly involving solvation differences in the free bases such as we have discussed elsewhere,[31] may be operating.

The +2.3 unit $\Delta\Delta pK_a$ value for *N*-(4-nitrophenyl)-aziridine in Table III is the term which we attribute to the change from sp^2 to sp^3 hybridization on the amine nitrogen in the free base. It may represent a minimal value, as we have not yet excluded one important base-weakening term, operating only with this single compound among the 4-nitroaniline derivatives studied. This effect, which involves strong solvent association with **3** (but not with **6**, although the latter is a stronger base), will be demonstrated and discussed in the following paper.[32]

It does not follow from the above conclusion that a hypothetical sp^3-hybridized *N*,*N*-dimethyl-4-nitroaniline would show as large a $\Delta\Delta pK_a$ value, since, as Bottini and Nash have suggested for *N*-phenylaziridine,[12] the three-membered ring in **3** may lead to even less orbital overlap with the ring π electrons than is normally the case with an sp^3 lone pair. We do estimate, however, that at least 1.0–1.5 of the 3.7–4.3 unit difference between pK_a's of corresponding aniline and 4-nitroaniline derivatives may be due to the change from sp^3 to sp^2 hybridization. Such effects may help explain the significantly larger ρ values for anilinium ion dissociations than are observed for phenols[2,3] and account in part for the multiplicity of σ values for both donor and acceptor substituents in Hammett-type correlations.[33] These matters will be discussed further in the following paper[32] and a rationale will be offered for the fact that most linear free-energy relationships involving aniline derivatives are indeed linear despite their neglect of the important hybridization term.

Experimental Section

Materials.—All materials were synthesized according to Suhr,[34,35] and recrystallized twice from methanol–water, with the exception of **3**, which was recrystallized from methanol–0.01 *N* aqueous sodium hydroxide to inhibit formation of ring-opened products and/or polymerization. The following melting points and analyses were obtained: *N*-(4-nitrophenyl)aziridine (**3**), mp 81–82° (lit.[34] mp 81.5–82°); *N*-(4-nitrophenyl)azetidine (**4**), mp 118–119° (lit.[34] mp 120–121°); *N*-(4-nitrophenyl)pyrrolidine (**5**), mp 167–168° (lit.[34] mp 166–167°); *N*-(4-nitrophenyl)piperidine (**6**), mp 101–102° (lit.[34] mp 105°); *N*-(4-nitrophenyl)hexamethylenimine (**7**), mp 76–77° (lit.[34] mp 76.3–77°); *N*-(2-hydroxyethyl)-4-nitroaniline, mp 108–110° (lit.[35] mp 111.9–112°).

Anal. Calcd for $C_8H_8N_2O_2$ (**3**): C, 58.53; H, 4.91; N, 17.06. Found: C, 58.21; H, 5.19; N, 17.39. Calcd for $C_9H_{10}N_2O_2$ (**4**): C, 60.65; H, 5.67; N, 15.72. Found: C, 60.33; H, 5.70; N, 15.99. Calcd for $C_{10}H_{12}N_2O_2$ (**5**): C, 62.47; H, 6.30; N, 14.58. Found: C, 62.21; H, 6.38; N, 14.89. Calcd for $C_{11}H_{14}N_2O_2$ (**6**): C, 64.05; H, 6.86; N, 13.58. Found: C, 63.96; H, 6.70; N, 13.83. Calcd for $C_{12}H_{16}N_2O_2$ (**7**): C, 65.42; H, 7.34; N, 12.72. Found: C, 65.66; H, 7.36; N, 12.99.

Uv Studies and Measurement of pK_a's.—Except for the measurements with **3**, which are discussed below, absorption spectra were obtained at 25.0 ± 0.1°, using 1-cm quartz cells with a Cary Model 14 recording spectrophotometer provided with a thermostated cell jacket. Previously described precautions were taken to guard against photochemical transformations.[36] Beer's law was applicable in all cases at the concentrations studied. Working solutions containing 1% methanol in the desired solvents were prepared from methanolic stock solutions and were in the range $2–8 \times 10^{-5}$ *M*.

To obtain spectra of the free bases, aliquot portions of the stock solutions were diluted into 1% sodium hydroxide; spectra of the anilinium ions were obtained by diluting into concentrated hydrochloric acid. pK_a's were determined at $\lambda_{max}^{1\%\ NaOH}$ and calculated from the equation

$$pK_a = pH \text{ (or } H_0) - \log [(A - A_1)/(A_2 - A)] \qquad (1)$$

where A is the absorbance of the solution of acidity corresponding to H_0 or pH, A_1 is the absorbance in concentrated acid, and A_2 is the absorbance in 1% sodium hydroxide.

Spectral data and average values for pK_a's of **1**–**7**, determined at three acidities for each compound, are listed in Tables I and II; the precisions, except in the case of **3**, were ±0.03 pK unit. Arnett and Mach[37] have shown that tertiary anilines in sulfuric acid; these values were used in the pK_a determinations of the tertiary amines.[38]

Uv Studies and pK_a Measurements on *N*-(4-Nitrophenyl)aziridine (3).—Because of rapid formation of ring-opened products [probably *N*-(2-hydroxyethyl)-4-nitroaniline accompanied by polymerization products][39] upon protonation of **3**, it was not possible to determine the pK_a of the corresponding aziridinium ion as above.

The accuracy of this pK_a determination was dependent on the accuracy with which we could determine the initial equilibrium concentration of the free amine upon addition to buffer. It was

(28) Another possible obtruding effect has not been excluded. Alkyl-ortho repulsions should tend toward destabilization of the anilinium ions. Relative to the dimethylanilinium ions, the effects should be base weakening in the case of the six-membered ring compounds (rigidity of the chair form), and base strengthening in the case of the three- and four-membered ring compounds. If these were taken into account, the $\Delta\Delta pK_a$ for **6** would be more positive, that for **3** less positive, and that for **4** more negative.

(29) The wide discrepencies in the reported data for the *N*-phenylpolymethyleneimines[4,9,12,30] (Table II) make the $\Delta\Delta pK_a$ values in this series somewhat suspect.

(30) G. Baddely, J. Chadwick, and H. T. Taylor, *J. Chem. Soc.*, 451 (1956).

(31) The discussion[5] involved the size of the water cluster solvating aniline as compared with its *N*-mono- and *N*,*N*-dialkyl derivatives. As applicable here, the argument might be that the constrained four- and five-membered rings allow closer approach or approach by a larger solvating cluster, with correspondingly greater free base stabilization.

(32) M. J. Kamlet, R. R. Minesinger, E. G. Kayser, M. H. Aldridge, and J. W. Eastes, *J. Org. Chem.*, **36**, 3852 (1971).

(33) H. van Bekkum, P. E. Verkade, and B. M. Wepster, *Recl. Trav. Chim. Pays-Bas*, **78**, 85 (1959).

(34) H. Suhr, *Justus Liebigs Ann. Chem.*, **689**, 109 (1965).

(35) H. Suhr, *ibid.*, **687**, 175 (1965).

(36) M. J. Kamlet and L. A. Kaplan, *J. Org. Chem.*, **22**, 576 (1957).

(37) E. M. Arnett and G. W. Mach, *J. Amer. Chem. Soc.*, **86**, 2671 (1964).

(38) As no values for H_0'', corresponding to secondary anilines, appear in the literature, values for H_0'' used in the pK_a calculation for *N*-(2-hydroxyethyl)-4-nitroaniline[39] were taken to be midway between those on the H_0' and H_0''' scales.

(39) The composition of the final product mixture formed on protonation of **3** and subsequent ring-opening appears to be variable and is probably concentration and pH dependent. While the spectrum corresponds closely to that of *N*-(2-hydroxyethyl)-4-nitroaniline, $\lambda_{max}^{1\%\ NaOH}$ 405 nm (ϵ 18,400), it is not solely the latter compound, as the apparent pK_a of one final reaction solution was measured to be −0.3, while the pK_a of an independently synthesized sample of *N*-(2-hydroxyethyl)-4-nitroaniline was observed to be −0.12.[38] Reactions at spectrophotometric concentrations preclude product isolation; however, such concentrations may favor production of *N*-(2-hydroxyethyl)-4-nitroaniline over polymeric species.

therefore necessary to obtain spectrophotometric data early in the reaction to obtain accurate extrapolation of optical densities back to zero time. The free aziridine appears to be sufficiently stable in 0.1 *N* NaOH to allow static measurements of optical density and extinction coefficient. No significant change in absorption was observed over a period of 20 min. However, at pH's near the pK_a of the ion, reaction is quite rapid and rapid-mixing techniques were necessary.

A spring-loaded rapid-mixing syringe, as designed originally by Gordon and Thompson[40] and modified by Burlinson and Kaplan,[41] was mounted atop the cell compartment of the Cary Model 14 spectrophotometer. A standard 2-ml hypodermic glass syringe with a 2-in no. 20 stainless steel needle was fitted to the end of a brass housing. The glass plunger was attached to a spring-loaded brass plunger within the housing. The syringe could be cocked and set to deliver rapidly any required volume up to 2 ml. The brass syringe holder was mounted vertically, directly above the mouth of the uv cell and at such a height that the tip of the needle was below the surface of the liquid in the absorption cell. The needle was bent slightly where it entered the cell to avoid the light path. A specially constructed 2.00-cm absorption cell with a wide and deep neck to accommodate the volume change upon injection was used. The syringe was calibrated by weight of water delivered, and found to deliver a volume increment to a precision of 0.500 ± 0.004 ml.

Our procedure consisted of monitoring the decrease with time (typical half-lives were 5–30 sec) in optical density at the wavelength of maximum absorption of the aziridine (325 nm) and, for a separate identical sample, the increase in optical density of the ring-opened product at its wavelength of maximal absorption (403 nm).[39] The completely reacted solution had an absorption tail extending to somewhat below 325 nm; it was therefore necessary to correct the observed absorbance at 325 nm for product to obtain the optical density due to free **3** only. At any given time, the observed optical density at 325 nm minus [the ratio of optical densities of the final product solution at 325 and 403 nm multiplied by the observed optical density (at 403 nm)] corresponded to the optical density due to the free aziridine [Az].

Since the total analytical concentration of species ([Az] + [AzH$^+$] + ring-opened product) was fixed, a plot of product optical densities at 403 nm *vs.* the corrected optical densities for free aziridine (at 325 nm) at corresponding times showed linear regression. When extrapolated back to zero product absorbance, *i.e.*, zero time, such a plot gave the initial optical density of free aziridine at the particular pH, from which the initial equilibrium concentration of aziridine could be calculated.[42]

The original formal concentration of **3** (= [Az] + [AzH$^+$]) being known, the difference between this and the initial equilibrium concentration of aziridine [Az] at the particular pH represents the initial equilibrium concentration of aziridinium ion [AzH$^+$]. With this data, the pK_a could be calculated from the equation

$$pK_a = pH - \log [Az]/[AzH^+] \quad (2)$$

(40) R. Thompson and G. Gordon, *J. Sci. Instrum.*, **41**, 480 (1964).

(41) N. Burlinson and L. A. Kaplan, U. S. Naval Ordnance Laboratory Report NOLTR 69-53, May 13, 1969.

(42) At the pH values in question, the ring-opened product was 99+% in the unprotonated form.[39]

To test the reliability of this method in furnishing the extinction coefficient of free aziridine by an extrapolated plot, a run was made at a pH of 4.00, which was sufficiently basic to assure essentially completely unprotonated **3** at zero time, and allowed reaction to proceed at a conveniently measurable rate (half-life about 6 min). The extrapolated extinction coefficient for free **3** was 10,960, compared with a statically determined value of 10,750 in 1% NaOH.

Because of extremely short reaction times below a pH of 2.20 (half-lives less than 5 sec), it was possible to obtain data only on *ca.* 2–6% protonated aziridine solutions even with the fast-mixing technique (spectrophotometer pen response and turbulence in the absorption cell preclude accurate data in the first 3–4 sec after mixing). Table IV lists pertinent data used in estimating the pK_a value for *N*-(4-nitrophenyl)aziridine in water at 25°. Because of the inherent uncertainties involved in calculating a pK_a from data at only 2–6% protonation, we have not taken an average of the results, but report only that there is a high probability that the pK_a for **3** falls between 0.9 and 1.2.

TABLE IV

DETERMINATION OF pK_a OF *N*-(4-NITROPHENYL)AZIRIDINE

pH	([Az] + [AzH$^+$]),[a] × 10^{-5} *M*	ϵ_{max} (corr)[b]	[Az],[c] × 10^{-1} *M*	[Az]/[AzH$^+$]	pK_a
2.20	5.11	10,127	4.81	16.0	1.0
2.50	4.64	10,506	4.53	41.2	0.9
2.70	5.06	10,524	4.95	45.0	1.0
2.70	4.92	10,569	4.84	60.5	0.9
2.80	4.83	10,455	4.79	36.2	1.2

[a] Initial formal concentration of **3**. [b] Extrapolated extinction coefficient at 325 nm, corrected for tail of band due to ring-opened species. [c] Calculated using 10,750 as the molar extinction coefficient of free aziridine.

Registry No.—**1**, 100-23-2; **2**, 2216-15-1; **3**, 30855-79-9; **4**, 31947-44-1; **5**, 10220-22-1; **6**, 6574-15-8; **7**, 13663-23-5.

Acknowledgment.—To be submitted to the American University by J. W. E. in partial fulfillement of requirements for the Ph.D. degree. We wish to thank Dr. L. A. Kaplan for helpful discussions and for assistance with the rapid-mixing techniques and Miss E. Kayser for running the nmr spectra. Support was furnished to J. W. E. by the U. S. Army Chief of Engineers and the staff of the Engineer Topographic Laboratories, Fort Belvoir, Va. A portion of the work was also done under U. S. Naval Ordnance Laboratory Independent Research Task IR-44.

Hydrogen Bonding by Hydroxylic Solvents to Aromatic Amines. Effects on Spectra and Relative Basicities of Some *N*-(4-Nitrophenyl)polymethylenimines

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Received March 11, 1971

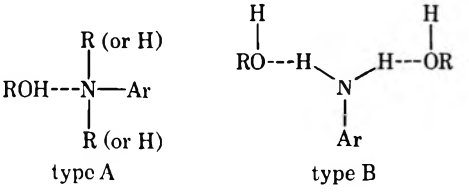
Linear interrelationships are found between the solvent shifts of the uv absorption maxima for near-sp² hybridized 4-$NO_2C_6H_4N$-$(CH_2)_n$, n = 3, 4, and 5, regardless of solvent type, *i.e.*, hydroxylic or nonhydroxylic.

The solvent shifts for *N*-(4-nitrophenyl)aziridine (n = 2), which is near-sp³ hybridized on the amine nitrogen, maintain the above linear interrelationships in nonhydroxylic media but deviate markedly in hydroxylic solvents; *i.e.*, the bathochromic shifts are all markedly smaller than expected. This indicates strong hydrogen bonding by hydroxylic solvents to the sp³-hybridized amine in contrast to the absence of such solvent association with the sp²-hybridized amines and would account, at least partially, for the anomalously low basicity observed for *N*-(4-nitrophenyl)aziridine. Displacements of nmr chemical shifts in going from nonhydroxylic to hydroxylic solvents appear to confirm these conclusions.

In the preceding paper,[1] uv and nmr spectra and pK_a's of some *N*-(4-nitrophenyl)polymethylenimine derivatives, 4-$NO_2C_6H_4N$-$(CH_2)_n$, with n = 2–6, were compared with data for *N*,*N*-dimethyl- (**1**) and *N*,*N*-diethyl-4-nitroaniline (**2**). From the uv and nmr spectra it was concluded that *N*-(4-nitrophenyl)aziridine (**3**) was near-sp³ hybridized at the amine nitrogen, while *N*-(4-nitrophenyl)azetidine (**4**), -pyrrolidine (**5**), and piperidine (**6**), as well as **1** and **2**, were near-sp² hybridized.[2]

The following pK_a's were reported: **1**, 0.65; **2**, 1.75; **3**, $0.9 < pK_a < 1.2$; **4**, 0.34; **5**, −0.42; **6**, 2.46. It came as somewhat of a surprise to us that, despite the difference in hybridization on the amine nitrogens (which, from *a priori* considerations, would have suggested that **3** should be a significantly stronger base),[3] the pK_a value for the aziridine was near the average for the nitroaniline derivatives studied. We therefore undertook to reexamine whether, in unraveling the various complex interacting phenomena contributing to the amine basicities, we had failed to take into account some important base-weakening effect on **3**. A specific solvent-association effect seemed a likely possibility.

We have mentioned[4] that two types of hydrogen bonding contribute to the total solvation picture involving aniline derivatives and hydroxylic solvents.[5–8] Type A, referred to as hydrogen bonding *by* solvent *to* substrate, leads toward ground-state delocalization of the electron pair on nitrogen, hence serving as a hypsochromic influence on the K band in the uv spectrum.[5] Such solvation had been considered to be increasingly significant the greater the base strength of the amine, and should be favored by sp³ hybridization. Type B, referred to as hydrogen bonding *to* solvent *by* substrate, serves toward charge concentration on the nitrogen, a bathochromic influence,[6–8] and would be expected to represent a greater proportion of total solvation with the more acidic sp²-hybridized amines. Either type of solvation should lower the free energy of the amine, and hence the anilinium ion pK_a; the type-A hydrogen bond, involving the better donor and acceptor, would be expected to have a significantly larger effect. Important base weakening by type-A hydrogen bonding has been suggested[4,9] in the cases of aniline and its *N*-alkyl and *N*,*N*-dialkyl derivatives.



Uv Spectra.—To test for type-A hydrogen bonding in the cases of **1** and **3**–**6**, we have determined their uv spectra in a series of 31 solvents, both hydroxylic and nonhydroxylic. Positions of the maxima are listed in Table I, together with values of $-\Delta\nu_{max}$, the bathochromic shifts (in kilokaisers) for each compound in each solvent relative to the spectrum of the same compound in cyclohexane. Plotted in Figure 1 are $-\Delta\nu_{max}$ values for **1**, **3**, **4**, and **6** as functions of the corresponding $-\Delta\nu_{max}$ values for *N*-(4-nitrophenyl)pyrrolidine (**5**), the least basic amine in the series.

It is seen that, in the plots for **1**, **4**, and **6**, bathochromic shifts for both hydroxylic (filled data points) and nonhydroxylic solvents (open data points) fall on the same straight lines which extend over a range of 4.3 kK (*ca.* 65 nm) between cyclohexane and water. Correlation is excellent; with the piperidine **6**, for example, least-squares analysis leads to the equation

$$\Delta\nu(6) = 0.005 + 1.018\Delta\nu(5) \quad (1)$$

(1) J. W. Eastes, M. H. Aldridge, R. R. Minesinger, and M. J. Kamlet, *J. Org. Chem.*, **36**, 3847 (1971).

(2) The numbering system is the same as in the preceding paper.[1] Numbers from **3** to **6** correspond to the size of the polymethylenimine ring.

(3) A referee has suggested that based on pK_a = *ca.* 6 for *N*-phenylaziridine [from the $\Delta\nu_{O-D}$ of hydrogen-bonded CH_3OD: T. Kagiya, Y. Sumida, and T. Inoue, *Bull. Chem. Soc. Jap.*, **41**, 767 (1968)], and assuming only modest conjugative interaction for the 4-nitro substituent, **3** would be predicted to have a pK_a near 3.

(4) J. W. Eastes, M. H. Aldridge, and M. J. Kamlet, *J. Chem. Soc. B*, 922 (1969).

(5) J. C. Deardon and W. F. Forbes, *Can. J. Chem.*, **38**, 896 (1960).

(6) J. H. P. Utley, *J. Chem. Soc.*, 3252 (1963); B. D. Pearson, *Proc. Chem. Soc.*, 78 (1962).

(7) R. R. Minesinger, E. G. Kayser, and M. J. Kamlet, *J. Org. Chem.*, **36**, 1342 (1971).

(8) M. J. Kamlet, *Israel J. Chem.*, **1**, 428 (1963).

(9) C. P. Nash and G. E. Maciel, *J. Phys. Chem.*, **68**, 831 (1964).

Table I

Ultraviolet Spectra of Some *N*-(4-Nitrophenyl)polymethylenimines

4-$NO_2C_6H_4R$

1, R = $-N(CH_3)_2$ 4, R = $-N-(CH_2)_3$

2, R = $-N(C_2H_5)_2$ 5, R = $-N-(CH_2)_4$

3, R = $-N-(CH_2)_2$ 6, R = $-N-(CH_2)_5$

Solvent	Compd	λ_{max}, nm	ν_{max}, kK	$-\Delta\nu_{max}$, kK[a]
C_6H_{12}	1	356.0	28.09	
	3	312.3	32.02	
	4	355.0	28.17	
	5	363.8	27.49	
	6	359.4	27.82	
CCl_4	3	317.3	31.52	0.50
	4	364.9	27.40	0.77
	5	372.5	26.85	0.64
	6	368.5	27.14	0.68
EtOEt	1	369.5	27.06	1.03
	3	319.0	31.35	0.67
	4	367.6	27.20	0.97
	5	377.4	26.50	0.99
	6	371.2	26.94	0.88
$(CH_3)_3CNH_2$	3	322.5	31.08	0.94
	5	384.0	26.04	1.45
	6	378.0	26.46	1.36
$CH_3COOC_2H_5$	3	324.5	30.82	1.20
	4	379.2	26.37	1.80
	5	386.8	25.83	1.66
	6	382.0	26.18	1.64
Tetrahydropyran	3	324.8	30.79	1.23
	5	385.7	25.93	1.56
	6	382.0	26.18	1.64
$Cl_2C{=}CHCl$	3	323.6	30.90	1.12
	5	386.9	25.85	1.64
	6	382.5	26.14	1.68
Dioxane	1	380.6	26.27	1.82
	3	324.8	30.79	1.23
	4	379.0	26.39	1.78
	5	387.8	25.79	1.70
	6	382.5	26.14	1.68
CH_3CCl_3	3	324.5	30.82	1.20
	5	387.8	25.79	1.70
	6	383.3	26.09	1.73
C_6H_6	3	326.0	30.67	1.35
	5	389.0	25.71	1.78
	6	384.5	26.01	1.81
$(CH_3)_3COH$	3	318.2	31.43	0.59
	5	390.2	25.63	1.86
	6	385.7	25.93	1.89
Tetrahydrofuran	3	327.5	30.53	1.49
	5	390.6	25.60	1.89
	6	386.1	25.90	1.92
$(CH_3)_2CHOH$	3	320.5	31.20	0.82
	4	385.1	25.97	2.20
	5	392.0	25.51	1.98
	6	387.3	26.82	2.00
CH_3CH_2OH	1	386.8	25.85	2.24
	3	321.2	31.13	0.89
	4	385.7	25.93	2.24
	5	393.0	25.45	2.04
	6	388.6	25.73	2.09
$CH_3{-}CO{-}CH_3$	1	390.2	25.63	2.46
	3	330.0	30.30	1.72
	4	390.1	25.63	2.54
	5	396.5	25.22	2.27
	6	392.5	25.48	2.34
CH_3OH	1	390.3	25.62	2.47
	3	321.5	31.10	0.92
	4	390.0	25.64	2.53
	5	397.1	25.18	2.31
	6	392.8	25.46	2.36
$CHCl_3$	3	327.3	30.55	1.47
	5	399.8	25.01	2.48
	6	395.0	25.32	2.50
$ClCH_2CH_2Cl$	3	331.6	30.16	1.86
	5	400.0	25.00	2.49
	6	395.8	25.27	2.55
$CH_3OCH_2CH_2OH$	3	328.5	30.44	1.58
	4	392.0	25.51	2.66
	5	399.0	25.06	2.43
	6	395.3	25.30	2.52
CH_2Cl_2	1	393.0	25.45	2.64
	3	330.0	30.30	1.72
	5	400.5	24.97	2.52
	6	396.0	25.25	2.57
CH_3CN	3	330.5	30.26	1.76
	5	401.5	24.91	2.50
	6	396.5	25.22	2.60
$ClCH_2CHCl_2$	3	333.5	29.98	2.04
	5	401.8	24.89	2.60
	6	397.5	25.16	2.66
Dimethylformamide	1	398.9	25.07	3.02
	3	336.2	29.74	2.28
	5	405.8	24.64	2.85
	6	402.5	24.84	2.98
$C_6H_5CH_2CH_2OH$	3	329.5	30.35	1.67
	5	410.0	24.39	3.10
	6	405.5	24.66	3.16
Sulfolane	3	338.5	29.54	2.48
	5	411.1	24.32	3.17
	6	406.5	24.60	3.22
$C_6H_5CH_2OH$	3	328.8	30.41	1.61
	5	412.5	24.24	3.25
	6	406.6	24.59	3.23
$C_6H_5OCH_2CH_2OH$	3	331.2	30.19	1.83
	4	405.0	24.69	3.48
	5	412.2	24.26	3.23
	6	407.2	24.56	3.26
$HOCH_2CH_2OH$	3	327.0	30.58	1.44
	4	405.0	24.69	3.48
	5	412.8	24.22	3.27
	6	408.0	24.51	3.31
$HOCH_2CH_2CN$	3	329.4	30.36	1.66
	4	410.0	24.39	3.78
	5	415.8	24.05	3.44
	6	411.5	24.30	3.52
CF_3CH_2OH	1	413.3	24.20	3.89
	3	309.0	32.36	−0.34
	4	415.9	24.04	4.13
	5	422.2	23.69	3.80
	6	419.4	23.84	3.98
H_2O	1	422.0	23.70	4.39
	2	430.0	23.26	
	3	323.5	30.91	1.11
	4	422.0	23.70	4.47
	5	431.7	23.16	4.33
	6	422.8	23.65	4.17

[a] Bathochromic shift relative to spectrum in cyclohexane.

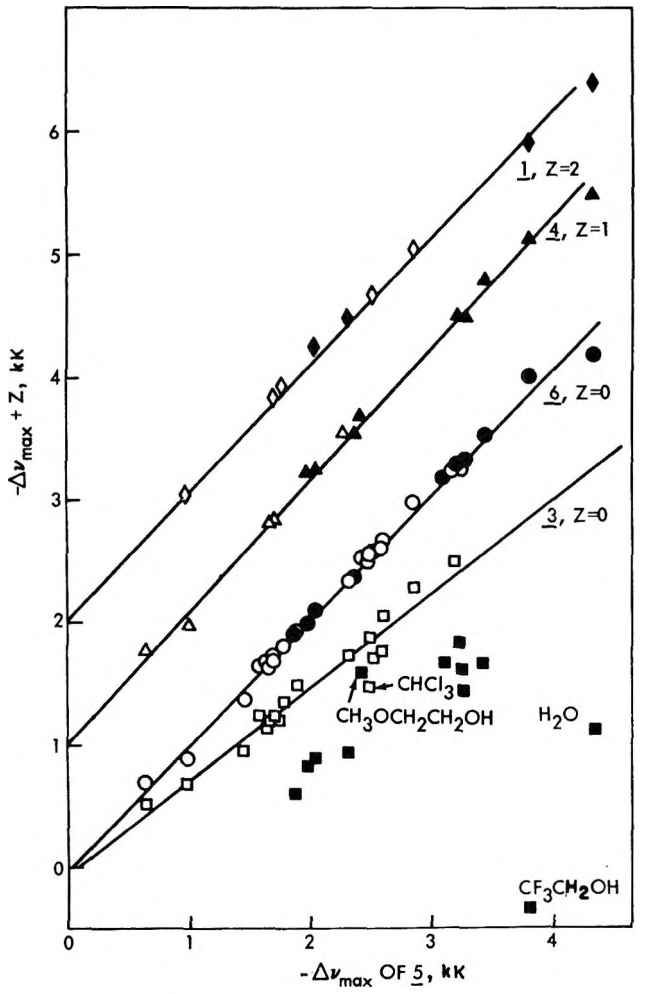


Figure 1.—Spectral shifts in various solvents plotted against corresponding shifts for *N*-(4-nitrophenyl)pyrrolidine (**5**): open data points, nonhydroxylic solvents; filled data points, hydroxylic solvents. The plots for **1** and **4** are displaced upward by 1.0 and 2.0 kK, respectively.

with r, the correlation coefficient, = 0.997 and s, the standard deviation, = 0.07 kK (*ca.* 0.5–1.0 nm). The plots for **1** and **4** show equally good linearity.[10]

A completely different type of situation obtains in the case of *N*-(4-nitrophenyl)aziridine (**3**). The $-\Delta\nu_{max}$ values for **3** in the nonhydroxylic solvents again show good linearity with corresponding $-\Delta\nu_{max}$ values for **5**, the correlation equation being

$$\Delta\nu(\mathbf{3}) = 0.059 + 0.772\Delta\nu(\mathbf{5}) \qquad (2)$$

with r = 0.989 and s = 0.095 kK. Here, however, the ROH solvents do not follow the trend established for the nonhydroxylic media. The data points for 10 of the 11 alcohols and for water fall off the plot by between *ca.* 6 and 30 standard deviations, and always in the direction of lower $-\Delta\nu_{max}$ values (less strongly bathochromic displacements). We take these strong deviations from the linearity observed in the other instances to be manifestations of the hypsochromic influences of type-A hydrogen bonding *by* these ROH solvents *to* **3**. The effect is so strong for **3** in trifluoroethanol that, despite the markedly more polar character of this solvent, the net result is a 3-nm *hypsochromic* shift relative to the spectrum in cyclohexane.

As rough quantitative measures of these hydrogen-bonding effects *by* the various solvents *to* **3**, we have calculated $\Delta\Delta\nu_{max}$ values, *i.e.*, the differences between observed $-\Delta\nu_{max}$ values and values calculated from eq 2. These are listed in Table II together with σ^* values for R in ROH.[11]

TABLE II

$\Delta\Delta\nu_{max}$ VALUES FOR *N*-(4-NITROPHENYL)AZIRIDINE IN VARIOUS HYDROXYLIC SOLVENTS

Solvent ROH	σ^* of R	$-\Delta\nu_{max}$ obsd, kK	$-\Delta\nu_{max}$ (eq 2), kK	$\Delta\Delta\nu_{max}$, kK
$(CH_3)_3COH$	−0.30	0.59	1.38	0.79
$(CH_3)_2CHOH$	−0.19	0.82	1.47	0.65
CH_3CH_2OH	−0.10	0.89	1.51	0.62
CH_3OH	0.00	0.92	1.72	0.80
$C_6H_5CH_2CH_2OH$	+0.08	1.67	2.33	0.66
$CH_3OCH_2CH_2OH$	+0.20	1.58	1.81	0.23
$C_6H_5CH_2OH$	+0.22	1.61	2.45	0.84
$HOCH_2CH_2OH$	+0.22	1.44	2.46	1.02
$C_6H_5OCH_2CH_2OH$	+0.30	1.83	2.43	0.60
$N{\equiv}CCH_2CH_2OH$	+0.46	1.66	2.60	0.94
HOH	+0.49	1.11	3.28	2.17
CF_3CH_2OH	+0.92	−0.34	2.87	3.21

It is evident that the data follow no quantitative Taft-type ρ–σ^* relationship[11] (possibly because of steric factors and varying size of the solvating cluster), but the trend does seem to be toward higher $\Delta\Delta\nu_{max}$ values (stronger solvation) the more acidic the ROH compound. It also appears that solvents capable of *intra*molecular hydrogen bonding (*e.g.*, $CH_3OCH_2CH_2OH$, $C_6H_5OCH_2CH_2OH$) show lower $\Delta\Delta\nu_{max}$ values than might be expected from their σ^*'s.[12]

Nmr Spectra.—We have also examined the nmr spectra of **1** and **3**–**6** in a number of solvents to ascertain whether a similar specific solvation effect involving only **3** is discernible by means of this probe. We had mentioned in our previous paper[1] that the nmr chemical shifts for the 2,6 protons are reasonably sensitive indicators of amine → ring mesomerism,[13] the greater the electron supply by the amine nitrogen, the less being the deshielding of the 2,6 protons by the 4-nitro group, and the lower the downfield shift. By extension of this reasoning, constraining the electron pair on the amine nitrogen in a type-A hydrogen bond should lead to less delocalization of charge to the ring, and therefore an increase in the downfield shift for the 2,6 protons.

A similar downfield shift as we go from nonhydroxylic to hydrogen-bonding solvents should also be observed for the *N*-methylene protons of **3**. The rational here would be that a type-A hydrogen-bonded amine nitrogen should be more effective at inductive electron withdrawal than its nonassociated counterpart.

Nmr spectral data for **1** and **3**–**6** in acetone-d_6, 11% D_2O–CD_3COCD_3, 20% D_2O–CD_3COCD_3, and trifluoroethanol are given in Table III. The results are

(10) Linearity was also observed in plots of $-\Delta\nu_{max}$ for **1**, **2**, and **4**–**6** *vs.* corresponding values with hydroxylic and nonhydroxylic solvents for 4-nitrotoluene, which appears to exclude specific solvation effects involving the amine groups in these nitroaniline derivatives. This will be discussed in greater detail in a subsequent paper.

(11) R. W. Taft, Jr., in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., Wiley, New York, N. Y., 1956, Chapter 13.

(12) It is also comment worthy that, of the nonhydroxylic solvents, chloroform shows the greatest deviation from the observed linearity. This may be because of the small amounts of ethanol stabilizer in Spectrograde chloroform. Small amounts of moisture in the other nonhydroxylic solvents may also account for the slightly greater scatter (and lower correlation coefficient) in the plot for **3** as compared with **1**, **4**, and **6**.

(13) I. D. Rae, *Aust. J. Chem.*, **18**, 1807 (1965); **20**, 2381 (1967).

TABLE III
NMR CHEMICAL SHIFTS FOR N-(4-NITROPHENYL)POLYMETHYLENIMINES IN VARIOUS SOLVENTS

Compd	CD_3COCD_3, δ, ppm	CD_3COCD_3/D_2O, 8/1, Δδ, ppm[a]	CD_3COCD_3/D_2O, 8/2, Δδ, ppm[a]	CF_3CH_2OH, Δδ, ppm[a]
		2,6 PROTONS[b]		
1	6.74	0.00	+0.01	−0.12
3	7.12	+0.05	+0.11	+0.03
4	6.32	+0.02	...[c]	−0.10
5	6.57	+0.03	+0.03	−0.12
6	6.92	0.00	+0.01	−0.18
		N-Methylene Protons		
1	3.13	0.00	+0.01	−0.08
3	2.23	+0.03	+0.08	+0.08
4	4.04[d]	+0.01	...[e]	...[e]
5	3.42[d]	+0.02	+0.01	−0.07
6	3.47[d]	0.00	+0.02	−0.06

[a] Displacements relative to spectra in acetone-d_6. [b] Midpoint of doublet; J_{HH} = *ca.* 10 cps. [c] Insoluble. [d] Triplet. [e] Obscured by solvent absorption.

presented in terms of δ values relative to TMS internal standard in the acetone-d_6 solvent and Δδ values (displacements relative to line positions in acetone-d_6) for the hydrogen-bonding solvents.

The data show the expected trends. As D_2O is added by increments to the deuterioacetone, both the 2,6 and the *N*-methylene proton signals of **1** and **4**–**6** show slight downfield shifts, but no consistent trends beyond experimental precision; with **3**, however, the downfield shifts are progressive, beyond experimental error, and unmistakable. The effects are more clearly shown in going from deuterioacetone to trifluoroethanol. Here, both sets of signals are shifted upfield in the cases of the sp^2-hybridized nitroaniline derivatives, but downfield only in the case of **3**.

These findings seem to offer strong corroborative evidence for the conclusions drawn from the uv studies. To evaluate the significance of the 0.11 ppm Δδ for **3** in going from deuterioacetone to 20% D_2O, the downfield displacement in the chemical shift for the 6 proton in *N*,*N*,2-trimethyl-4-nitroaniline relative to the 2,6-proton signal of **1** is 0.19 ppm. Hence, the hydrogen-bonding effect is of the same order of magnitude as is an effect resulting from significant steric inhibition of resonance.[14]

Conclusions

Both the uv and the nmr results serve as strong evidence that, of the nitroaniline derivatives studied, only the pyramidally hybridized aziridine derivative **3** undergoes significant type-A hydrogen bonding by hydroxylic solvents, despite the fact that **6** is a stronger base in water than **3** by 1.3–1.6 p*K* units. It is tempting to conclude, therefore, that hybridization on the amine nitrogen is a factor which influences type-A hydrogen bonding more strongly than "intrinsic" basicity.

The above comparison is not completely fair without qualification, however, since the pK_a of **3** in water already incorporates the base-weakening effect of this solvent stabilization of the free amine. The fairer test would involve relative pK_a's of **3** and **6** in a non-hydroxylic solvent. Unfortunately, such a comparison is precluded by the rapid acid-catalyzed ring-opening reaction of **3**, which makes measurement of its basicity extremely difficult.[1]

It would be valuable, therefore, to be able to evaluate the extent of the base weakening by this solvation effect for **3** and other pyramidally hybridized aromatic amines in water. Little information toward this end is available; estimates in the case of near-sp^3-hybridized aniline and its *N*,*N*-dialkyl derivatives have ranged from several tenths to about 1.0 p*K* unit,[4,9] and the three-membered ring in **3** might make the value somewhat greater.[15] How much greater, however, is at present impossible to assess, and we must leave the quantitative aspects of this problem involving **3** unresolved.

These, and our earlier findings regarding hybridization effects on amine basicities,[1] lead to some interesting speculation regarding Hammett-type ρ–σ correlations and other linear free-energy relationships for aromatic amines. At one end of a Hammett series, *i.e.*, with positively substituted aniline derivatives, we have near-sp^3 hybridization (base strengthening) and strong free base solvation (base weakening). At the other end, with the negatively substituted aniline derivatives, we have near-sp^2 hybridization (base weakening) and little or no solvent stabilization of the free amine. Individually, these base-strengthening and base-weakening effects could account for respectable proportions of the 5.0 unit difference between 4-methoxy- and 4-nitroanilinium ion pK_a's. *That ionization constants in the aniline or dialkylaniline series show good ρ–σ correlation may therefore be an accidental consequence of the fact that the hydrogen-bonding and hybridization effects tend to just about cancel one another out.*[16,17] The multiplicity of σ values which have been noted for both donor and acceptor substituents in other Hammett-type correlations[18] may arise from situations where such extraneous effects do not quite offset one another (*e.g.*, as would be the case for most reactions in nonhydroxylic solvents).

Experimental Section

Preparations, physical properties, and analyses for the materials used here were given in the preceding paper.[1] Ultraviolet absorption spectra were determined on a Cary Model 14 recording spectrophotometer with matched 1-cm silica cells. Concentrations were 3–5 × 10^{-5} *M*. Previously described precautions were taken to guard against photochemical transformations.[19] Nmr spectra were determined on a Varian HA-100 spectrometer, using internal TMS as a reference standard.

Registry No.—**1**, 100-23-2; **2**, 2216-15-1; **3**, 30855-79-9; **4**, 31947-44-1; **5**, 10220-22-1; **6**, 6574-15-8.

(14) The angle of twist of the dimethylamine group in *N*,*N*-2-trimethyl-4-nitroaniline is *ca.* 40° (unpublished information).

(15) Overlap between the amine lone pair and the ring π system is probably less here than in normally sp^3-hybridized amines with *ca.* 109° valence angles.[1]

(16) The reasoning here might be considered circuitous on the basis that the anilinium ion pK_a's provide part of the information used to derive the σ^- values for the −*M* substituents in the Hammett equation. The same conclusion can be derived, however, by comparing pK_a's of anilinium ions and phenols, where analogous changes in hybridization and solvation on oxygen are unlikely.

(17) Another possibility, that hybridization and solvation on the amine nitrogens also vary progressively with σ has not been ruled out. This would require, however, that we go from near-sp^3 hybridization in aniline to $sp^{>3}$ hybridization in *p*-hydroxy- or *p*-methoxyaniline, and we consider this possibility the less likely.

(18) H. van Bekkum, P. E. Verkade, and B. M. Wepster, *Recl. Trav. Chim. Pays-Bas*, **78**, 85 (1959).

(19) M. J. Kamlet and L. A. Kaplan, *J. Org. Chem.*, **22**, 576 (1957).

Acknowledgment.—To be submitted to the American University by J. W. E. in partial fulfillment of requirements for the Ph.D. degree. We wish to thank Drs. L. A. Kaplan, T. N. Hall, and H. G. Adolph for helpful discussions. Support was furnished to J. W. E. by the U. S. Army Chief of Engineers and the staff of the Engineer Topographic Laboratories, Fort Belvoir, Va. A portion of the work was done under U. S. Naval Ordnance Laboratory Independent Research Task IR-44.

Nucleophilic Substitution at an Acetylenic Carbon. Kinetics of the Reaction between Bromoacetylene and Triethylamine in Dimethylformamide[1]

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Received April 21, 1971

Isolation of ethynyltriethylammonium bromide and chloride was achieved in the reaction between triethylamine and the respective monohaloacetylenes (1) in dry ether. The kinetics of the same reaction was studied in dimethylformamide (DMF). Because of the ready decomposition of 1 in air, a conductometric method of following the formation of 2 in a closed, oxygen-free system was devised. This conductance method could be used for kinetics in the range $[HC{\equiv}CBr]_0 = 0.002$–$0.004\ M$ and gave consistent rates for $[(C_2H_5)_3N]_0 < 0.4\ M$. Higher concentrations of triethylamine, which lowered the dielectric constant of the medium, also reduced the rate of salt formation. The activation parameters for this second-order reaction are $\Delta H^{\ddagger} = 11.8$ kcal/mol and $\Delta S^{\ddagger} = -43$ eu. Several reaction paths to 2 can be discounted easily, but a choice between paths a *vs.* c and i in Scheme I cannot be made.

Although there is considerable interest in the properties of the haloalkynes, no kinetic study on any of the parent compounds HC≡CX has been carried out.[2,3] Undoubtedly, the proclivity of these simple halides to burn, explode, or decompose on contact with oxygen may have been a factor. In our exploration of the scope of nucleophilic substitution at an acetylenic carbon,[2] we now examine process 1. When this

$$\underset{1}{HC{\equiv}CBr} + (C_2H_5)_3N \longrightarrow \underset{2}{HC{\equiv}CN(C_2H_5)_3}{}^{+}\,Br^{-} \xrightarrow{(C_2H_5)_3N} [\underset{3}{HC{\equiv}CN(C_2H_5)_2}] + \underset{4}{(C_2H_5)_4N^{+}Br^{-}} \quad (1)$$

work was started, the chemistry of ynamines was just being developed. Now, these are familiar reagents,[4] although their salts are still rare.[5] The first results on process 1 were, in fact, incidental to a study of the dehydrobromination of 1,2-dibromoethylene by triethylamine in DMF.[6] In this study we isolated 2 and obtained the kinetics of and restricted the mechanistic alternatives in reaction 1.

(1) (a) Supported in part by the National Institutes of Health, Grant GM 7021; (b) Abstracted from the Ph.D. thesis of R. T., Illinois Institute of Technology, 1970.

(2) (a) G. R. Ziegler, C. A. Welch, C. E. Orzeeh, S. Kikkawa, and S. I. Miller, *J. Amer. Chem. Soc.*, **85**, 1648 (1963); (b) C. E. Orzech, C. A. Welch, G. R. Ziegler, J. I. Dickstein, and S. I. Miller, *ibid.*, **84**, 2020 (1962); (c) A. K. Kuriakose, and S. I. Miller, *Tetrahedron Lett.*, 905 (1962); (d) H. G. Viehe, S. I. Miller, and J. I. Dickstein, *Angew. Chem.*, **76**, 537 (1964); (e) A. Fujii, J. I. Dickstein, and S. I. Miller, *Tetrahedron Lett.*, 3435 (1970); (f) A. Fujii and S. I. Miller, *J. Amer. Chem. Soc.*, **93**, 3694 (1971); (g) R. Tanaka, M. Rodgers, R. Simonaitis, and S. I. Miller, *Tetrahedron*, **27**, 2651 (1971); (h) J. I. Dickstein and S. I. Miller, unpublished results; (i) R. Tanaka and S. I. Miller, *Tetrahedron Lett.*, 1753 (1971).

(3) S. Y. Delavarenne and H. G. Viehe in "The Chemistry of Acetylenes," H. G. Viehe, Ed., Marcel Dekker, New York, N. Y., 1969, Chapter 10.

(4) (a) H. G. Viehe, ref 3, Chapter 12; (b) J. Ficini and C. Barbara, *Bull. Soc. Chim. Fr.*, 2787 (1965); (c) S. R. Sandler and W. Karo, "Organic Functional Group Preparations," Academic Press, New York, N. Y., 1971, Chapter 4.

(5) J. L. Dumont, *C. R. Acad. Sci.*, **261**, 1710 (1960).

(6) W. K. Kwok, W. G. Lee, and S. I. Miller, *J. Amer. Chem. Soc.*, **91**, 468 (1969).

Experimental Section[1b]

Purified DMF,[6] bp 58° (30 mm), was redistilled over Linde 13X Molecular Sieves directly into a special solvent reservoir, in which it could be stored and from which it could be dispensed through Teflon tubing and syringe needles, always under dry nitrogen. An ir spectrum of the purified DMF (0.1 mm) showed no detectable water absorption (<0.05%). An nmr (neat) spectrum had no foreign peaks. The specific conductance at 25° was well below 10^{-6} ohm^{-1} cm^{-1} (lit.[7] 0.4–2.7 × 10^{-7} ohm cm^{-1}), which was the limit of measurement of our conductance bridge. Triethylamine, purified as described previously,[6] was checked and stored in the same way as DMF. Diethylamine was dried over potassium hydroxide, then fractionally distilled under nitrogen.

Bromoacetylene (1).[8]—This substance is dangerous and may burn or explode on contact with air; it was prepared, transferred, and stored under dry nitrogen.[6] The bromoacetylene generator was connected to a line which consisted of a bubbler containing aqueous potassium hydroxide, a column (2.5 × 30 cm) of calcium chloride, four U-traps, a receiver, and a bubbler (air seal). 1,2-Dibromoethylene was added dropwise to a solution of ethanolic sodium hydroxide and brought to reflux temperature. The monobromoacetylene was carried into the line by a stream of nitrogen and purified by trap-to-trap distillation, until it was finally condensed into the flask at −78° containing the solvents (15 g of DMF or 45 ml of ethyl ether).

For kinetic runs, the solution of 1 (*ca.* 1.2 *M*) in DMF was diluted *ca.* 10 times with DMF under nitrogen and stored in Dry Ice. For preparative runs, the ether solution was mixed directly with triethylamine under nitrogen.

Chloroacetylene (1′).[8]—Chloroacetylene is even more dangerous than bromoacetylene, because it is as reactive and much more volatile. It was generated from *cis*-1,2-dichloroethylene in essentially the same way as described above.

Reaction between Bromoacetylene and Diethylamine.—Bromoacetylene was introduced into a flask containing diethylamine (8 ml) 6 in anhydrous ether (45 ml) at −78°. This flask was brought to ~25°, venting occasionally to relieve excess pressure. After the solution was stirred magnetically for 24 hr, the white solid was filtered off under nitrogen, and the filtrate was concentrated under nitrogen to give a yellow oil (~1 ml). The ir spectrum of the solid precipitate was identical with that of authentic diethylamine hydrobromide. As for the liquid product, since it was unstable and decomposed during distillation,

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(8) L. A. Bashford, H. J. Emeleus, and H. V. A. Briscoe, *J. Chem. Soc.*, 1358 (1938).

an elemental analysis was not obtained and spectral data were obtained on the crude oil. It contained halogen and is tentatively identified as *cis*-2-bromo-1-diethylaminoethylene. In the ir spectrum, the presence of bands at 1638, 1618 (sh), and 1260 cm^{-1} and the absence of bands at ~960 cm^{-1} indicated an analog of *cis*-dibromoethylene.[9] In the nmr spectrum, there was an apparent AX quartet of cis alkene protons consisting of two strong inner peaks and two weaker outer peaks: nmr (DMSO-d_6) δ 1.50 (t, J = 7.0 Hz), 3.18 (q, J = 7.0 Hz), 4.44 (d, J = 6.3 Hz), and 6.37 (d, J = 6.3 Hz).

Ethynyltriethylammonium Bromide (2).—To a stock solution of 1 in anhydrous ether (45 ml) at −78°, triethylamine (10 ml) was added with a hypodermic syringe. The system was brought to ~25° and stirred magnetically for 48 hr; inspection of the ir spectrum of the ether solution indicated that even after 24 hr a substantial amount of 1 remained. The volume of solution was reduced in a dry nitrogen stream and then pushed by nitrogen pressure directly from the flask through a sintered glass filter in which an off-white solid was collected. The filtrate was swept with nitrogen to remove ether, leaving only a minute amount of yellow oil, whose nmr (CCl_4) and ir (neat) spectra indicated *N*,*N*-diethylacetamide[6] and triethylamine. To remove traces of a dark impurity, the precipitate (*ca.* 500 mg) was repeatedly dissolved in Spectrograde acetonitrile (0.5–1 ml) in a stoppered flask equipped with a built-in glass filter, reprecipitated with anhydrous ether, and filtered off under nitrogen pressure. Finally, the solid was placed under high vacuum for 2 days and stored under nitrogen in the dark. It had ir (KBr) 3085 ($\nu_{HC\equiv}$), 2138 ($\nu_{C\equiv C}$), 1460, 1408, 1308, 1010 and 995 cm^{-1}; nmr (DMSO-d_6) δ 1.36 (t, 9 H, J = 7.3 Hz), 3.82 (q, 6 H, J = 7.3 Hz), and 4.86 (s, 1 H); mp 107–108° dec; mass spectrum *m/e* 110 and 108 ($C_2H_5Br^+$), 101 [$(C_2H_5)_3N^+$], 97 [$(C_2H_5)_2NC{\equiv}CH^+$], 86 (101 − 15), 82 (97 − 15), 54 ($C_4H_6^+$), 41 ($C_2H_3N^+$), 29 ($C_2H_5^+$).

Anal. Calcd for $C_8H_{16}BrN$: C, 46.61; H, 7.82. Found: C, 46.09; H, 7.87.

This solid could not be filtered in the open without rapid deliquescence and formation of a tar-like brown slurry. Nevertheless, the solid did not seem to react with water under neutral conditions. The ir spectrum of the tar resulting from the interaction of water and the solid was a superposition of the component spectra; the nmr spectrum in DMSO-d_6 of the dry solid was identical with that of its aqueous solution.

Compound 2 gave a positive Beilstein test and its aqueous solution with silver nitrate deposited silver bromide. When an alcoholic solution of 2 was added dropwise to an alkaline solution of potassium iodide and mercuric chloride mixture, precipitation of a bright yellow solid, possibly $I^-(C_2H_5)_3N^+C{\equiv}CHgI$, occurred: mp 157–158° from acetonitrile–water; ir (KBr) 1450, 1380, and 995 cm^{-1}; nmr (DMSO-d_6) δ 1.39 (t, J = 7.1 Hz) and 3.86 (q, J = 7.1 Hz); the mass spectrum had peaks for HgI_2^+, HgI, I_2^+, Hg^+, I^+, and *m/e* 156 ($C_2H_5I^+$), 128 (HI), 124 ($C_8H_4N^+$), 113 ($C_7H_{15}N^+$), 105 ($C_7H_7N^+$), etc.

When 2 (100 mg) was heated at 80° in an ampule with triethylamine (*ca.* 1 ml) for 2 hr and the mixture was worked up, a dark solid, chiefly 4, and an oil, chiefly, *N*,*N*-diethylacetamide, were identified by their spectra.[6] Several attempts to isolate or detect the ynamine 3 itself failed; for example, 2 and triethylamine were heated at 50° for 12 hr, they were refluxed in ether for 24 hr, or the reaction was carried out in hexamethylphosphoramide at 25°. At no stage of the above conditions could 3 be detected by spectral means.[4] Instead, an unidentified polymeric resin, which showed an ir absorption at 1670 cm^{-1}, was invariably obtained along with tetraethylammonium bromide and *N*,*N*-diethylacetamide.

Conductometric Kinetics.—A General Radio impedance bridge type 650-A, equipped with a General Radio unit oscillator which supplied 1000-cps alternating current between a pair of 4-kohm resistors at both terminals, was used. The null point on the Wheatstone bridge was detected by an oscilloscope.

Our conductance cells were constructed of glass in an H shape. The sides (legs) had ground glass caps fitted with stopcocks, and the platinum electrodes (10 × 10 mm) were set 10 mm apart in one leg. Since they were used only in nonaqueous solvents, the platinum black on the electrodes was removed by electropolishing.[10] The cells were washed thoroughly with water and methanol, dried, and filled repeatedly with pure DMF, until $R > 10^6$ ohms. To decide on the best concentration range for this study, we investigated the conductance ($1/R$) of triethylammonium bromide (0–0.12 M) in DMF–triethylamine. Conventional Kohlrausch plots ($1/[Br^-]R$ *vs.* $[Br^-]^{1/2}$) had variable negative slopes, large at low and small at high concentrations.[10,11] Fortunately, $1/R$ was linear in $[Br^-]$ in the limited range 0.002–0.004 M in DMF,[7] in which $R \cong 10^4$–10^3 ohms (Figure 1).

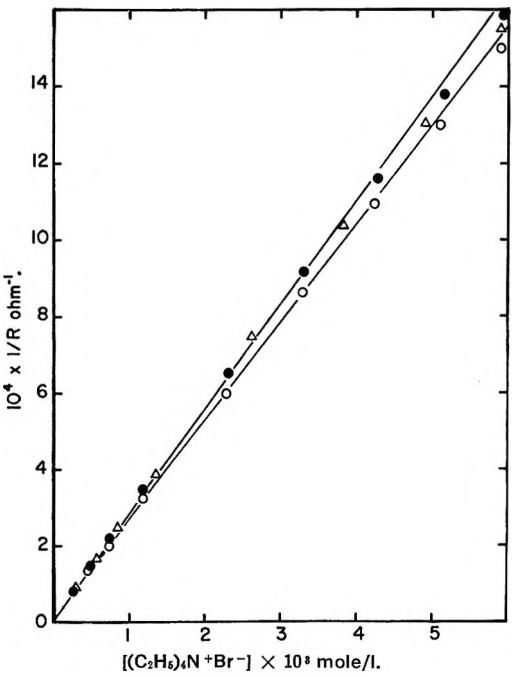


Figure 1.—The conductance of tetraethylammonium bromide in DMF–triethylamine solutions: $[(C_2H_5)_3N]$ ●, 0.1; △, 0.2; ○, 0.3 mol/l.

For the kinetic runs, all glassware was dried and flushed with nitrogen. Solvents and solutions were transferred wholly under nitrogen when possible; pipet transfers were made quickly against a stream of nitrogen. Our stock solution of bromoacetylene (~0.12 M) in DMF was diluted to ~0.048 M and a stock solution of triethylamine (2.00 M) in DMF was prepared. The DMF, which had been soaking the electrodes, was drained from the conductance cell. The air in the conductance cell was swept out for *ca.* 2 hr with nitrogen, and the right and left legs were loaded in turn with known volumes of the reactant solutions to make up a final volume of 20.0 ml. The cell was immersed in a constant-temperature bath. After 5–10 min, it was removed from the bath, inverted and shaken vigorously, tilted so that all of the solution collected in the electrode compartment, and quickly replaced in the bath. Four such cells were usually set up together. At intervals up to 12 hr, R was taken from 10^6–1800 ohms; R_∞ was obtained in 3–5 days.

Under pseudo-first-order conditions of $[(C_2H_5)_3N]_0 \gg [HC{\equiv}CBr]_0$, and subject to the linearity assumption $1/R \propto [Br^-]$, second-order kinetics in process 1 leads to expression 2. Rate constants (k_ψ) could be obtained from "linear" plots of the type

$$k_\psi t = \ln[R/(R - R_\infty)] + \ln(1 - R_\infty/R_0) \qquad (2)$$

given in Figure 2; the early points were neglected because of the uncertainties in R at low $[Br^-]$. The rate law 2 was tested over a modest range in concentrations; reproducibility is evident from several pairs of initially identical runs (Table I). The results of a comparable number of runs are not given here: at the start of this work, 24 runs in the nonlinear range of $1/R$ were made; in addition, runs with inconsistent trends in R occasionally turned up, because of leaks in the system, problems with the electrodes, or for undetermined causes.

In order to correct the concentrations for volume changes of

(9) J. M. Dowling, P. G. Puranik, A. G. Meister, and S. I. Miller, *J. Chem. Phys.*, **26**, 233 (1957).

(10) T. Shedlovsky in "Techniques of Organic Chemistry," A. Weissberger, Ed., 3rd ed, Vol. I, Wiley-Interscience, New York, N. Y., 1959, p 3036.

(11) "Du Pont DMF Product Information," Industrial and Biochemicals Department, E. I. du Pont de Nemours & Co., Wilmington, Del., 1967, pp 3, 31.

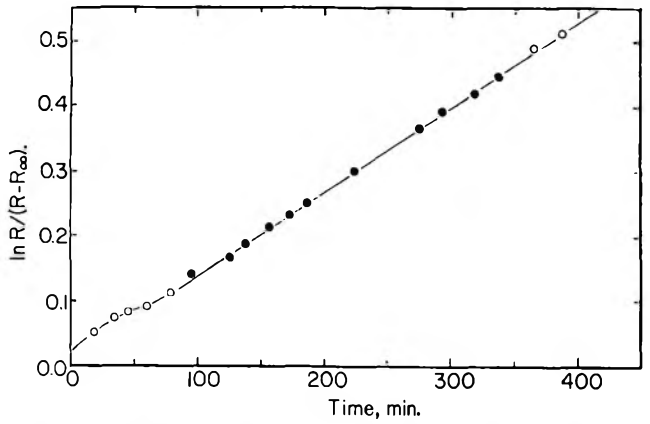


Figure 2.—The reaction of bromoacetylene ($[HC{\equiv}CBr]_0$ = 0.0024 M) with triethylamine ($[(C_2H_5)_3N]_0$ = 0.4 M) in DMF at 81.30 ± 0.1°; k_ψ was obtained from the shaded points.

TABLE I

CONDUCTOMETRICALLY DETERMINED PSEUDO-FIRST-ORDER RATE CONSTANTS (k_ψ) OF THE BROMOACETYLENE–TRIETHYLAMINE REACTION IN DIMETHYLFORMAMIDE

Temp, °C ± 0.1	$[(C_2H_5)_3N]_0$, mol/l.	$[HC{\equiv}CBr]_0$, mol/l.	$k_\psi \times 10^4$, min^{-1}
60.00	1.00	0.0024	9.124
60.00	1.00	0.0024	9.466
60.00	0.50	0.0024	5.720
60.00	0.50	0.0024	5.947
59.99	0.30	0.0024	3.708
60.02	0.20	0.0013	2.038
60.02	0.20	0.0013	2.667
71.46	0.50	0.0024	11.56
71.50	0.50	0.00052	16.49[a]
71.45	0.30	0.0024	5.356
71.45	0.20	0.0024	4.816
71.45	0.10	0.0024	3.767[a]
71.59	1.00	0.0024	16.956
71.59	0.70	0.0024	12.397
71.57	0.40	0.0024	8.497
71.57	0.30	0.0024	6.575
71.57	0.20	0.0024	4.677
71.53	0.50	0.0024	10.672
71.46	0.40	0.0024	7.874
81.30	0.50	0.0024	15.58
81.30	0.40	0.0024	12.91[b]
81.30	0.20	0.0024	13.20[a]
81.24	0.30	0.0024	10.07
81.24	0.30	0.0024	11.10
81.24	0.20	0.0024	8.38
81.24	0.20	0.0024	8.26
81.36	0.10	0.0017	4.333
81.36	0.20	0.0024	7.546
81.26	0.20	0.0024	7.211
81.26	0.10	0.0024	4.162

[a] Not included in Figure 3. [b] This run is illustrated in Figure 2.

the medium, we used eq 3 for the density (d) variation with temperature (t, °C),[11,12] and assumed that the volumes of triethylamine and DMF were additive. Plots of k_ψ *vs.* the temperature-corrected values of $[(C_2H_5)_3N]$ are displayed in Figure 3. The linear portions (<0.5 M) of these curves represent the region of second-order kinetics of process 1, and the least-squares slopes

$$d(\mathrm{DMF}) = 0.9445 - 0.000872\,(t - 25)$$
$$d[(C_2H_5)_3N] = 0.73255 - 0.00091\,(t - 15) \quad (3)$$

(12) M. J. Timmermans and Hennault-Roland, *J. Chim. Phys.*, **29**, 529 (1932).

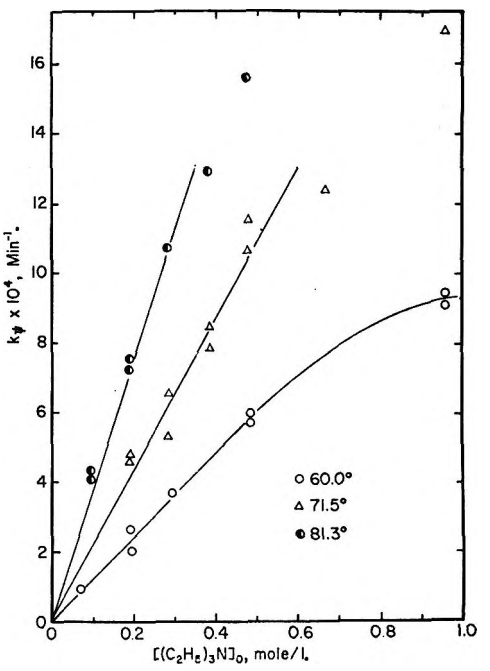


Figure 3.—Pseudo-first-order rate constants of bromoacetylene–triethylamine reaction *vs.* initial triethylamine concentrations.

($\Delta k_\psi/\Delta[(C_2H_5)_3N]$) yield the second-order rate constants (Table II). Activation parameters were obtained from standard expressions.[6]

According to the specifications of our conductance bridge, the uncertainty in R is 1%. A single reading in R could lead to an uncertainty in k_ψ of ~20%; for our typical run of about 10 points, this would be reduced to 6–7%; for a set of runs at one temperature, this would be cut to 3–4% in the final k value. In Table II, we simply give the probable errors calculated through the least square-fit of data given in Table I.

Titrimetric Kinetics.—Stock 1 in DMF and triethylamine (100.0 ml) were transferred in a nitrogen-filled glove bag to a volumetric flask (250 ml) and made up to volume with DMF. The flask was well shaken and removed from the glove bag, and aliquots (100 ml) were dispensed into nitrogen-flushed ampules, which were then capped. All of the ampules were cooled in Dry Ice–acetone until they were sealed. Apart from those ampules reserved for the "blank" estimate of bromide, the ampules were either left in constant-temperature baths for various times or otherwise stored at −78°. For analysis, the ampules were opened, rinsed into glacial acetic acid (7 ml), and titrated with standard silver nitrate.

By using an excess of triethylamine, we could show that process 1 followed pseudo-first-order kinetics. Under these conditions, it was not essential to know $[HC{\equiv}CBr]$ at time zero. This was fortunate, since each run appeared to have a characteristic and large bromide blank (~15%) which presumably arose from the absorption of oxygen during the preparation of the solutions and filling of the ampules at *ca.* 25°. Nevertheless, pseudo-first-order plots were obtained (Figure 4). The second-order constants, k, were obtained from $k_\psi/[(C_2H_5)_3N]$ (Table III).

Chloroacetylene and Triethylamine.—A reaction in ether similar to that in the previous section was carried out for chloroacetylene, but for 64 hr at ~25°. The white solid had spectra virtually identical with those of **2**. This compound was difficult to purify and no acceptable elemental analysis was obtained. Preliminary kinetic runs by the conductimetric method indicated that **1** and **1′** reacted at comparable rates, with the chloro compound slightly slower than the bromo compound. Since k_ψ and $[(C_2H_5)_3N]_0$ were inconsistent in these first runs, we could only estimate k.

Results and Discussion

Stoichiometry and Kinetics.—At 25° in ether, the product of process 1 is the ynamine salt **2**. (This incidentally is the parent of this class of compounds.)

TABLE II

SELECTED RATE DATA FOR THE REACTION OF ORGANIC BROMIDES AND AMINES

System	Solvent	Temp, °C	$k \times 10^5$, M^{-1} sec^{-1}	$\Delta H^{\pm}$, kcal mol^{-1}	$\Delta S^{\pm}$, eu	Ref
$HC{\equiv}CBr + (C_2H_5)_3N$	DMF	60.0	2.00 ± 0.06	11.8 ± 0.2	−43 ± 1	*a*
		71.5	3.72 ± 0.13			
		81.3	6.14 ± 0.18			
$C_2H_5Br + (C_2H_5)_3N$	$(CH_3)_2CO$	100	55			*b*
	C_6H_6	100	5			*b*
n-$C_3H_7Br + (CH_3)_3N$	C_6H_6	80.5	17.8	11.0	−44.9	*c*
$H_2C{=}CHBr + C_5H_{10}NH$	$C_6H_5NO_2$	100	0 (100 hr)			*d*
trans-*p*-$C_7H_7SO_2CH{=}CHBr + C_6H_{11}NH_2$	CH_3OH	25.0	198			*e*
$C_6H_5Br + C_5H_{10}NH$	C_6H_6	130	0 (200 hr)			*f*
p-$C_6H_5SO_2C_6H_4Br + C_6H_{10}NH$	C_6H_6	120	0.18	15.7	−45.6	*f*

[a] This work. [b] Reference 14. [c] C. A. Winkler and C. N. Hinshelwood, *J. Chem. Soc.*, 1147 (1935). [d] G. Salomon and A. J. Ultée, Sr., *Recl. Trav. Chim. Pays-Bas*, 69, 95 (1950). [e] S. Ghersetti, G. Lugli, G. Melloni, G. Modena, P. E. Todesco, and P. Vivarelli, *J. Chem. Soc.*, 2227 (1965). [f] F. Kalberer, *Bull. Soc. Fribourg. Sci. Nat.*, 44, 225 (1954); *Chem. Abstr.*, 50, 16718 (1956).

TABLE III

TITRIMETICALLY DETERMINED KINETIC DATA FOR THE REACTION BETWEEN BROMOACETYLENE AND TRIETHYLAMINE (2.8575 *M*) IN DIMETHYLFORMAMIDE

Temp, °C ± 0.1	$[HC{\equiv}CBr]_0$[a] mol/l.	$k_\psi \times 10^2$, min^{-1}	$k \times 10^3$,[b] l. mol^{-1} min^{-1}
59.55	0.123	0.650	2.36
59.50	0.0847	0.698	2.54
59.66	0.0522	0.510	1.85[c]
59.81	0.0636	0.627	2.28
78.85	0.123	1.17	4.35
78.95	0.0847	1.137	4.23
79.32	0.0522	0.99	3.68[c]
79.28	0.0636	1.013	3.77
79.58	0.0333	0.856	3.18
79.45	0.0115	0.705	2.62
101.00	0.123	1.95	7.44
102.00	0.0847	1.955	7.45
102.18	0.0522	1.73	6.60[c]
102.36	0.0333	1.619	6.17
102.20	0.135	3.10	10.83[d]

[a] Taken from $[Br^-]_\infty$. [b] The correction for solvent expansion was made. At the three temperatures, the mean k's are 2.2 ± 0.02, 3.6 ± 0.5, and 6.6 ± 0.5 × 10^{-3} M^{-1} min^{-1}; if plots of k *vs.* $[HC{\equiv}CBr]_0$ are extrapolated to $[HC{\equiv}CBr]_0 = 0$, the k's are 0.45, 2.4, and 4.5 × 10^{-3} M^{-1} min^{-1}. [c] The actual run is shown in Figure 4. [d] Single value from ref 6.

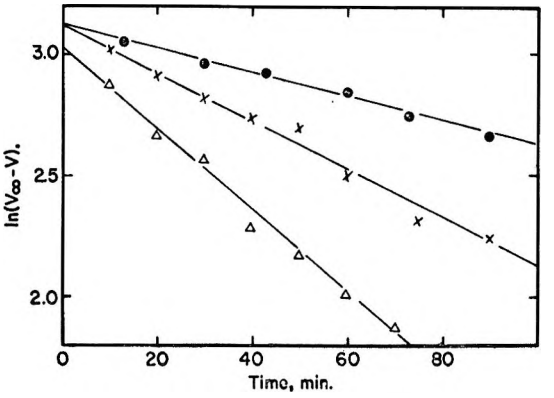
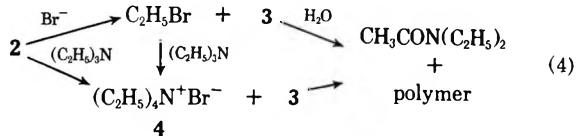


Figure 4.—The reaction of bromoacetylene (*ca.* 0.68 *M*) with triethylamine (2.96 *M*) in DMF at 59.66° (●), 79.32° (×), and 102.18° (△). *V* is the volume of silver nitrate (0.0264 *M*).

At 80° in triethylamine, **2** is converted into **4**. Although we were unable to isolate **3**, its hydration product, *N*,*N*-diethylacetamide, was identified (eq 4). Previously, neither **2** nor **3** were detected[6] from this reaction, although **3** has been prepared in impure form by a different route from trichloroenamines.[4b] Strenuous efforts were made to exclude moisture, but some amide is always formed. The deliberate or inadvertent use of an ynamine as a desiccant has precedent.[2d,h,4] With less hazardous haloalkynes, scaling up may be a useful synthetic strategy so that relatively small quantities of product may be sacrificed to remove traces of water from the reagents and apparatus.[3]

Whether the final products are formed along the top or bottom branch of eq 4 is not established by this



(4)

work. Judging by its quaternization rate, a path *via* ethyl bromide is not precluded (Table II).[13] These "relative rates" for the two steps were determined under synthetic conditions, that is, in ether, in which **2** is essentially insoluble. In our kinetic solvent, DMF, the salts were soluble; in any case, DMF is more polar than ether and the rate of the second step (SN2) relative to the first (AdN2) should be enhanced.[14,15]

The kinetics of process 1 were followed conductometrically in the absence of air in the "low" triethylamine region (Table I). The reaction was first order in bromoacetylene and in triethylamine (Figures 2 and 3). The various derived quantities are collected in Table II. The large negative $\Delta S^{\pm}$ is characteristic of the reactions between neutral molecules to form charged species (Table II).[2f,16] Incidentally, bromoacetylene is both neutral and nonpolar ($\mu \cong 0$).[17]

Since two salts, **2** and **4**, could have been present in our product mixtures, it may appear that a rate law based on one salt could lead to problems. The fact that eq 2 was obeyed indicates that, if **2** and **4** were both present, their equivalent conductances were similar. This is also plausible, since the equivalent conductances of related salts can be close: Λ $[(C_2H_5)_4$-

(13) N. Menschutkin and M. Wassilieff, *Z. Physik. Chem.*, **5**, 589 (1890).
(14) A. J. Parker, *Chem. Rev.*, **69**, 1 (1969).
(15) (a) E. Tommila, *Acta Chem. Scand.*, **13**, 622 (1959); (b) M. H. Abraham, *Chem. Commun.*, 293 (1970).
(16) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," 2nd ed, Wiley, New York, N. Y., 1965, p 138.
(17) H. Jones, N. L. Owen, and J. Sheridan, *Nature*, **213**, 175 (1967).

NBr] = 81.71 and Λ [$(CH_3)_4NBr$] = 82.90 ohm cm^{-1} at 0.16 *M* in DMF at 25°.[7b,18] If this picture is correct, our rate data refer to the first step of eq 1 despite the fact that the second step, **2** → **3**, may be relatively slow.

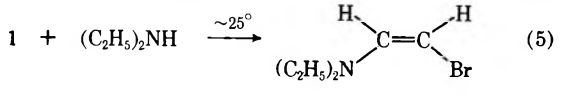
Process 1 was also followed titrimetrically at "high" triethylamine (2.86 *M*). Of necessity, there was some exposure of the solutions to air in the preparation of the kinetic runs. This led to substantial bromide ion blanks, before the samples were placed in the constant-temperature baths. Besides this, there were difficulties in treating the rate constants, which increased with [HC≡CBr]$_0$. For this reason, both a *k* value, obtained by extrapolation to [HC≡CBr]$_0$ = 0, and a mean *k* were estimated (Table III). Judging by the data of Figure 4, there does not appear to be any pronounced ionic strength effect during individual runs. We tentatively associate difficulties in the titrimetric *k*'s with an "oxygen effect" which leads to both rapid and delayed conversions of bromoacetylene to bromide ion.

Although they cannot be weighted equally, it is interesting to compare the *k*'s obtained in the two concentration ranges of triethylamine. Judging from the trends in Table I, the conductometric *k*'s at 2.86 *M* triethylamine ($\epsilon \cong 6.5$) should be low. The plots in Figure 3 presumably reflect the fact that added triethylamine (ϵ = 2.14), decreases both the polarity of the solvent DMF (ϵ = 28.1) and the rate of quaternization.[15] These expectations are borne out by the extrapolated, but not the average, conductometric *k*'s at 60 and 80° which tend to be "low" (Table III).

Mechanism.—Concerning process 1, the first mechanistic question concerns the point of attack, namely on bromine, α carbon, or β carbon. There is, in fact, evidence for the *triphilic* character of haloalkynes, that is, the conversion of phenylbromoacetylene by methoxide in methanol to phenylacetylene, phenyl methoxyacetylene (and *E*-β-bromo-β-methoxystyrene), and *Z*-β-bromo-α-methoxystyrene.[2g] Indeed, attack on bromine with amine nucleophiles is known both in the alkane[19] and alkyne series,[2d,h,3] and with some nucleophiles, *e.g.*, tributylphosphine or sodium diethylphosphite, bromine abstraction from an sp carbon may predominate.[2e] As for attacks on the carbon atoms in the simple alkylbromoalkynes, these do occur, but the choice between them is equivocal.[3,4]

In Scheme I, we give several mechanistic alternatives. However relevant these may be in other systems, most can be discarded here. As we shall see, two survive by default and because of simplicity.

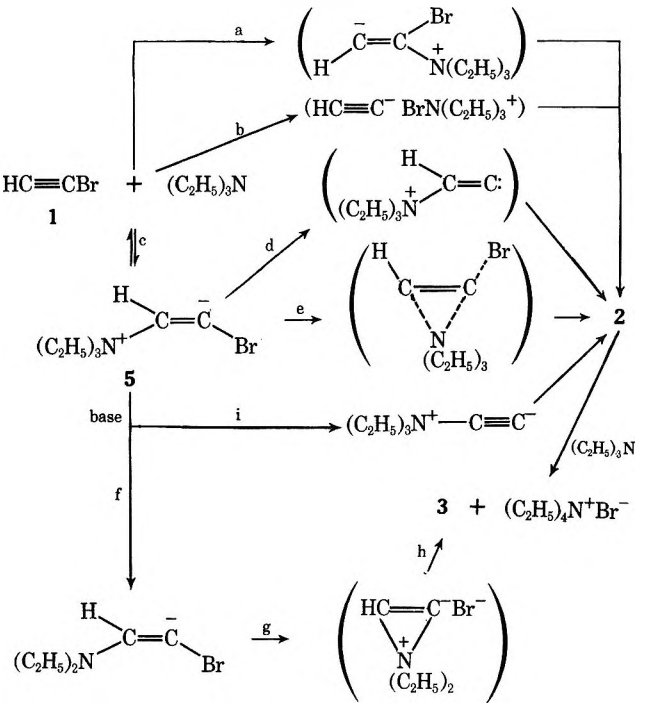
The addition of diethylamine to **1** (eq 5) under mild



(5)

conditions was intended to provide a model for the formation of **2**. If it was a model, this was not obvious, since diethylamine attacked the β carbon. A similar result has been reported for 1-bromohexyne, in which 1,2-bisdiethylaminohexene-1 is the isolable product.[20] It does appear that secondary amines attack the α carbon of 1-bromo-3,3-dimethylbutyne-1 or 1-bromo-3-methylpentyn-3-ol to give low yields of 1,1-bisaminoalkene-1 or the related amide, but these are not really convincing models for process 1.[20,21]

SCHEME I



Attack on bromine similar to that of step b of Scheme I is excluded, since the ion pair [HC≡C⁻BrHN-$(C_2H_5)_2$⁺] almost certainly should lead to acetylene.[2e-h,3,4,21]

The formation of the β adduct in eq 5 makes path c plausible in Scheme I. Although step e is known in the Fritsch–Buttenberg–Wiechell rearrangement,[22] here the necessary syn elimination would be unfavorable; in addition there is no precedent for the 1,2-anionic rearrangement of a quaternary nitrogen.[23] Step f seems to be unexceptional and the subsequent rearrangement (g, h) has precedent in examples provided by Viehe, *et al.*[24] There is, however, the problem of going from **3** to **2**; because triethylamine is a stronger base (nucleophile) than **3**, the direction shown in Scheme I, namely **2** → **3**, is preferred.

The concerted 1,2 rearrangement in **5** of a hydrogen (or alkyl) group to anionic carbon (not shown) never occur—at least, reported examples turn out to be nonconcerted[25]—and moreover are unlikely for orbital symmetry reasons.[26] If, however, **5** sheds bromide ion along d to give a carbene, then the 1,2-hydride shift to **2** need not be forbidden. Again, the anti dehydrobromination along step i, followed by proton uptake, also leads to **2** and seems intuitively more attractive than d, under our reaction conditions. This group of

(18) R. D. Singh, P. P. Rastogi, and R. Gopal, *Can. J. Chem.*, **46**, 3525 (1968).

(19) I. M. Mathai, K. Schug, and S. I. Miller, *J. Org. Chem.*, **35**, 1733 (1970).

(20) V. Wolf and H. Piater, *Justus Liebigs Ann. Chem.*, **696**, 90 (1966).

(21) (a) V. Wolf and F. Kowitz, *ibid.*, **638**, 33 (1960); (b) V. Wolf, W. Block, and H. Piater, *ibid.*, **682**, 112 (1965).

(22) G. Köbrich, *Angew. Chem.*, **79**, 15 (1967).

(23) D. V. Banthorpe in "The Chemistry of the Amino Group," S. Patai, Ed., Interscience, New York, N. Y., 1968, Chapter 10.

(24) S. Y. Delavarenne and H. G. Viehe, *Chem. Ber.*, **103**, 1198, 1209, 1216 (1970).

(25) U. Schöllkopf, U. Ludwig, G. Ostermann, and M. Patsch, *Tetrahedron Lett.*, 3415 (1969); U. Schöllkopf, J. Schossig, and G. Ostermann, *Justus Liebigs Ann. Chem.*, **737**, 158 (1970).

(26) S. I. Miller, *Advan. Phys. Org. Chem.*, **6**, 195 (1968).

mechanisms cannot apply generally, of course, since a mobile group such as hydrogen is essential. Realistically, we believe we are left with steps a or c and i in Scheme I as alternate mechanisms in this system.

Rate Comparisons.—In Table II we have collected rate data for Menschutkin substitutions of differing types of organic bromides. Were it necessary, one could estimate the rate constant for triethylamine with ethyl bromide in DMF.[13,15] It should be appreciated that any comparison of reactivity of saturated with unsaturated centers involves a comparison of an SN2 with an AdN2 process. Our preliminary and generally qualitative comparisons[6] stand up here: k (alkyl) $\cong$ k (ethynyl) $\gg$ k (vinyl) $\gg$ k (aryl).

Registry No.—1, 593-61-3; 2, 31883-95-1; triethylamine, 121-44-8; dimethylformamide, 68-12-2; tetraethylammonium bromide, 71-91-0.

Carbodiimide–Sulfoxide Reactions. XIII.[1] Reactions of Amines and Hydrazine Derivatives

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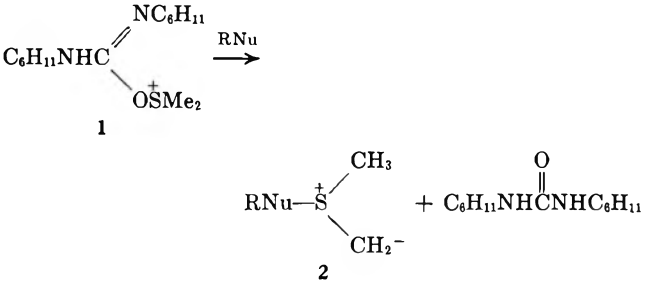
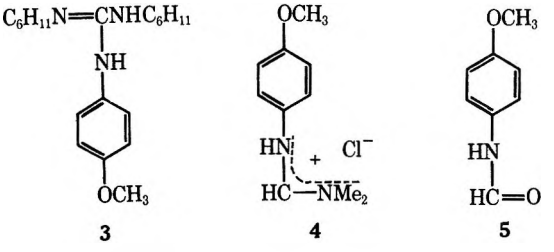
Received June 1, 1971

The acid-catalyzed reactions of a variety of amines and hydrazine derivatives with DMSO and DCC have been examined. Mildly basic aromatic amines such as nitroanilines readily react to form *N*-aryl-*S*,*S*-dimethylsulfilimines in high yield. The reaction of 2,4-dinitrophenylhydrazine leads to a variety of products arising *via* initial formation of the corresponding aryldiimide and aryldiazonium salt. Some reactions of methylthio(2,4-dinitrophenyl)diimide are reported. Acylhydrazides are largely converted into *N*,*N*′-diacylhydrazines, probably *via* the acyldiimides. A more complex array of products results from the reaction of an acylhydrazide with DMSO and phosphorus pentoxide. Sulfonylhydrazides lead ultimately to the formation of thiolsulfonates presumably *via* disproportionation of an intermediate sulfinic acid. The reaction of benzophenone hydrazone leads to the formation of diphenyldiazomethane which subsequently reacts further to give a number of products. Benzil dihydrazone gives as its major product diphenylacetylene. Indole slowly gives 3-(methylthiomethyl)indole which is partially converted into 3,3′-bisindolylmethane. Mechanisms are considered for all these types of reactions.

Previous papers in this series have described the mild, acid-catalyzed reactions of alcohols,[3] phenols,[4] enols,[5] oximes,[6] carboxylic and hydroxamic acids,[7] carboxylic acid amides,[7] and sulfonamides[1] with dimethyl sulfoxide (DMSO) and dicyclohexylcarbodiimide (DCC). These varied types of reactions can all be explained by initial formation of a DMSO–DCC adduct (1) which undergoes reaction with the appropriate nucleophile to form a sulfonium ylide (2) which can subsequently collapse or rearrange in a number of ways. Formation of the ylide 2 can occur either directly *via* a concerted cyclic process[8] or in two steps by facile loss of a proton from the corresponding sulfonium compound.



Since all the DMSO–DCC reactions we have examined have been found to require acidic catalysis, we felt that an extension of the above studies to amines as the reactive nucleophile might be difficult. This seemed particularly so since at an early stage we examined the reaction with 2,4-dinitroaniline, an amine that we felt might be sufficiently weakly basic to not block the acid-catalyzed formation of 1. This compound showed no reaction whatsoever by tlc and an essentially quantitative yield of unreacted amine was recovered in crystalline form. A more strongly basic amine, *p*-anisidine, also failed to undergo any interesting reaction and was instead shown to undergo simple addition to DCC forming 1,3-dicyclohexyl-2-(4-methoxyphenyl)guanidine (3). The formation of 3 was



previously observed during preparation of nucleoside 5′-phosphoroanisidates, the latter compounds being isolated as their salts with this guanidine.[9] Since DMSO did not appear to be involved in the formation of 3, a comparable reaction was carried out between *p*-anisidine, DCC, and anhydrous phosphoric acid in dimethylformamide (DMF). A totally different reaction then occurred giving *N*-(4-methoxyphenyl)-*N*′,*N*′-dimethylformamidine, which was isolated as its

(1) For Part XII, see U. Lerch and J. G. Moffatt, *J. Org. Chem.*, **36**, 7314 (1971).

(2) Syntex Postdoctoral Fellow, 1966–1968.

(3) (a) K. E. Pfitzner and J. G. Moffatt, *J. Amer. Chem. Soc.*, **87**, 5661, 5670 (1965). (b) For a review see J. G. Moffatt in "Techniques and Applications in Organic Synthesis: Oxidation," Vol. 2, R. Augustine and D. J. Trecker, Ed., Marcel Dekker, New York, N. Y., 1971 p1.

(4) (a) M. G. Burdon and J. G. Moffatt, *J. Amer. Chem. Soc.*, **88**, 5855 (1966); (b) M. G. Burdon and J. G. Moffatt, *ibid.*, **89**, 4725 (1967).

(5) A. F. Cook and J. G. Moffatt, *ibid.*, **90**, 740 (1968).

(6) A. H. Fenselau, E. H. Hamamura, and J. G. Moffatt, *J. Org. Chem.*, **35**, 3546 (1970).

(7) U. Lerch and J. G. Moffatt, *ibid.*, **36**, 3686 (1971).

(8) J. G. Moffatt, *ibid.*, **36**, 1909 (1971).

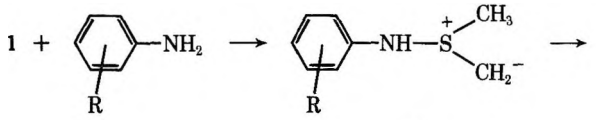
(9) J. G. Moffatt and H. G. Khorana, *J. Amer. Chem. Soc.*, **83**, 649 (1961).

crystalline hydrochloride **4** in 88% yield. During attempted crystallization of the free base of **4** from aqueous methanol, considerable hydrolysis occurred giving 4-methoxyformanilide (**5**).

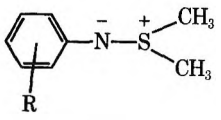
The formation of formamidines through condensations of DMF with amines in the presence of phosphorus oxychloride,[10] sulfonyl chlorides,[11] etc., is well known and the present experiment suggests that DMF can also be activated by reaction with DCC.

While the results with both 2,4-dinitroaniline and *p*-anisidine were disappointing, other aromatic amines of intermediate basicity reacted quite differently. Thus, *p*-nitroaniline, *m*-nitroaniline, and 3,5-dinitroaniline all reacted rapidly with DMSO, DCC, and anhydrous phosphoric acid at room temperature to give the corresponding crystalline *S,S*-dimethyl-*N*-arylsulfilimines (**7a–c**) in 74–85% yields. This type of compound has only recently become known through the work of Claus and Vycudilik,[12] who have reacted a number of aromatic amines with DMSO and phosphorus pentoxide in the presence of triethylamine. Both the *m*-nitro- and *p*-nitrophenylsulfilimines (**7a,b**) were prepared by this route, but the isolated yields of 37 and 35% are much lower than those using DMSO and DCC. By tlc examination it is clear that other aromatic amines such as α-naphthylamine also react with DMSO and DCC to form sulfilimines, but these compounds are rather unstable and undergo partial decomposition to the parent amine during work-up.

The formation of sulfilimines no doubt occurs *via* attack of the amine on **1** to form the sulfonium ylide **6**, which then undergoes a proton shift to form the more stable product **7**. Once again, we cannot at this time rule out the alternative possibility that concerted reaction of the amine with **1** gives a sulfonium salt rather than the ylide **6**, facile loss of an NH proton then giving the sulfilimine.

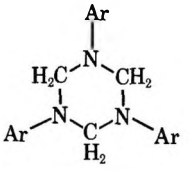


6

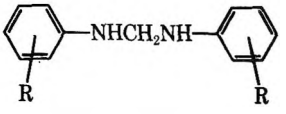


7a, R = *p*-NO_2
b, R = *m*-NO_2
c, R = 3,5-diNO_2

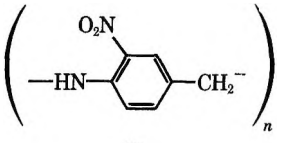
It is interesting to note that we too had examined the reactions of several aromatic amines with DMSO and phosphorus pentoxide, only without the addition of triethylamine. Under these conditions sulfilimines were not formed. Thus, reaction of *p*-nitroaniline with DMSO and phosphorus pentoxide at room temperature gave a highly insoluble, crystalline product which appears to be a polymer resulting from condensation of the amine with formaldehyde. The presence of an $-NCH_2N-$ grouping was clearly apparent from the nmr spectrum of the product, and its mass spectrum showed the monomeric unit $NO_2C_6H_4NCH_2$ as its largest fragment. Since the product shows no NH stretching vibrations in its infrared spectrum, we suggest that it is the cyclic trimer **8**, although we cannot exclude a linear polymer. As early as 1892 Pulvermacher[13] reported that condensation of *p*-nitroaniline with formaldehyde in ethanol gives *N,N'*-bis(*p*-nitrophenyl)methylenediamine (**9a**) with mp 232°, and this same product has also been obtained by different routes.[14,15] We have repeated and confirmed the original preparation,[13] obtaining analytically pure **9a** that was clearly different from the product from the DMSO–P_2O_5 reaction, particularly by the presence of an intense NH stretching band at 3500 cm^{-1} in its infrared spectrum. Similarly, the reaction of *o*-nitroaniline with DMSO and phosphorus pentoxide gave a polymeric material that was identical with the "polymeric anhydro-3-nitro-4-aminobenzyl alcohol" (**10**) prepared according to Meyer and Rohmer.[16] The structure of this compound has been deduced by its hydrolysis with strong acid to 3-nitro-4-aminobenzyl alcohol[16] and is consistent with its nmr spectrum in which the aromatic proton adjacent to the nitro group appears as a doublet showing only meta coupling. The absence of ortho coupling clearly shows that the aromatic ring is substituted at the 4 position. Finally, the reaction of 2,4-dinitroaniline with DMSO and P_2O_5 gives, in 82% yield, a crystalline product which from its elemental analysis must be *N,N'*-bis(2,4-dinitrophenyl)methylenediamine (**9b**).



8, Ar = *p*-$NO_2C_6H_4$



9a, R = *p*-NO_2
b, R = 2,4-diNO_2



10

The formation of **8**, **9**, and **10** must be a consequence of the decomposition of DMSO to formaldehyde in the presence of phosphorus pentoxide. It is not clear, however, why the three nitroanilines above should give different types of formaldehyde adducts. The totally different reaction path observed in the presence of triethylamine[12] is probably due to both the absence of protonation of the aniline amino group and a suppression of the decomposition of DMSO to formaldehyde.

We next turned our attention to the reactions of hydrazine derivatives and found that 2,4-dinitrophenylhydrazine (**11**) rapidly reacted with DMSO, DCC, and anhydrous phosphoric acid with evolution of

(10) H. Bredereck, R. Gompper, K. Klemm, and H. Rempfer, *Chem. Ber.*, **92**, 837 (1959).

(11) N. Steiger, U. S. Patent 3,184,482 (1965); *Chem. Abstr.*, **63**, 5564 (1965).

(12) (a) P. Claus and W. Vycudilik, *Tetrahedron Lett.*, 3607 (1968); (b) P. Claus and W. Vycudilik, *Monatsh. Chem.*, **101**, 396, 405 (1970).

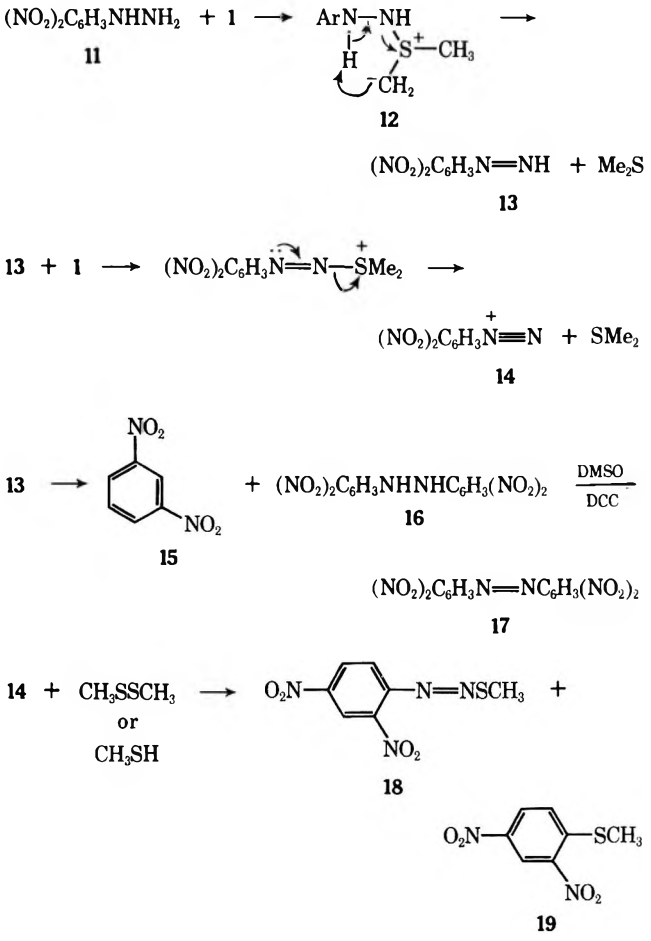
(13) G. Pulvermacher, *Ber.*, **25**, 2762 (1892).

(14) C. J. Pederson, *J. Org. Chem.*, **23**, 255 (1958).

(15) H. Zinner and H. Wigert, *Chem. Ber.*, **94**, 2209 (1961).

(16) J. Meyer and M. Rohmer, *Ber.*, **33**, 250 (1900).

nitrogen. From the complex mixture of products three crystalline substances were isolated and shown to be *m*-dinitrobenzene (**15**, 29%), 2,4-dinitrophenyl methylsulfide (**19**, 11%),[17] and 2,2′,4,4′-tetranitroazobenzene (**17**, 2%).[18] A similar reaction between **11**, DMSO, and phosphorus pentoxide also gave **15** (5%) and **19** (31%) and, in addition, a 13% yield of a crystalline compound identified as methylthio(2,4-dinitrophenyl)diimide (**18**). All of these compounds could arise *via* the intermediacy of either 2,4-dinitrophenyldiimide (**13**) or 2,4-dinitrophenyldiazonium ion (**14**) and formation of the latter compounds can be rationalized as follows.



In the above sequence, intramolecular proton abstraction and collapse of the intermediate sulfonium ylide **12** leads directly to 2,4-dinitrophenyldiimide (**13**). Based upon the work of Kosower, *et al.*,[19] upon the reactions of aryldiimides, **13** would be expected to spontaneously decompose to **15** and 2,2′,4,4′-tetranitrohydrazobenzene (**16**), probably *via* radical processes. As will be seen later, the hydrazobenzene **16** would be rapidly oxidized to **17** by DMSO and DCC. The oxidation of phenylhydrazine to phenyldiimide, and decomposition of the latter, has been achieved using lead tetraacetate and other reagents.[20]

On the other hand, the diazosulfide **18**, and perhaps the sulfide **19**, would appear more likely to arise from the diazonium salt **14**. As early as 1884 Stadler[21] demonstrated the formation of diazosulfides from aryldiazonium salts and mercaptans, and subsequently these compounds have been further studied.[22] The presence of the diazonium ion **14** during reaction of **11** with DMSO and phosphorus pentoxide was supported by the isolation, in 39% yield, of the known azo dye, 4-(2,4-dinitrophenylazo)-1-naphthol,[23] in the presence of 1-naphthol. The diazosulfide **18** was independently prepared by reaction of 2,4-dinitrophenyldiazonium fluoroborate[24] with dimethyl disulfide, and **19** was chromatographically identified as another major product. The disulfide was used in this reaction since mercaptans are known to be very rapidly oxidized to the corresponding disulfides by DMSO and DCC.[3b,25] Since the decomposition of DMSO to methyl mercaptan and formaldehyde seems to be promoted much more readily by phosphorus pentoxide than by DCC, the absence of **18** in the reaction of **11** with DMSO and DCC is probably due to a shortage of the mercaptan. In support of this it was shown that addition of excess dimethyl disulfide to a reaction as above with DCC led to the isolation of **18** in 20% yield. Similarly, the yield of **18** was raised to 43% in the phosphorus pentoxide reaction by addition of dimethyl disulfide, while dimethyl sulfide had no effect. Treatment of 2,4-dinitrophenyldiazonium tetrafluoroborate with DMSO and phosphorus pentoxide was shown by tlc to give the methyl sulfide **19** as the major product.

Several simple reactions of the diazosulfide **18** were also examined. In the presence of acid, **18** appears to decompose with formation of the diazonium ion **14**. Thus, treatment of **18** at room temperature with a solution of hydrogen chloride in dioxane in the presence of 1-naphthol gave 4-(2,4-dinitrophenylazo)-1-naphthol in 78% yield. Thermal decomposition of **18** took place upon heating without solvent at 140° and gave the methyl sulfide **19** in 72% yield together with smaller amounts of **15** (3%) and bis(2,4-dinitrophenyl)-sulfide (5%).[26] Smooth decomposition of **18** with loss of nitrogen also occurred upon heating its solution in dimethylformamide at 160° but under these conditions the yield of **19** was reduced to 25 and 27% of **15** was isolated. Thermal decomposition of aryldiazosulfides has previously been shown to lead to aromatic hydrocarbons, sulfides, and disulfides, presumably *via* radical pathways.[22]

Addition of a slight excess of bromine to a solution of **18** in chloroform at 0° led to almost instantaneous decolorization and evolution of nitrogen. From this reaction crystalline 2,4-dinitrobromobenzene (**22**)[27] was isolated in 96% yield. It is likely that this reaction proceeds *via* initial formation of the bromosulfonium compound **20** followed by dissociation into nitrogen and the aryl cation **21** and recombination with bromide ion.

Hydrazobenzene (**23**) reacted rapidly with DMSO

(17) R. W. Bost, J. O. Turner, and R. D. Norton, *J. Amer. Chem. Soc.*, **54**, 1985 (1932).

(18) A. S. Bailey, M. Maung, G. W. F. Orpwood, and J. E. White, *Tetrahedron*, **22**, 995 (1966).

(19) (a) E. M. Kosower, P. C. Huang, and T. Tsuji, *J. Amer. Chem. Soc.*, **91**, 2325 (1969); (b) P. C. Huang and E. M. Kosower, *ibid.*, **90**, 2367 (1968).

(20) J. B. Aylward, *J. Chem. Soc. C*, 1663 (1969), and references cited therein.

(21) O. Stadler, *Ber.*, **17**, 2075 (1884).

(22) H. Van Zwet and E. C. Kooyman, *Recl. Trav. Chim. Pays-Bas*, **86**, 993, 1143 (1967).

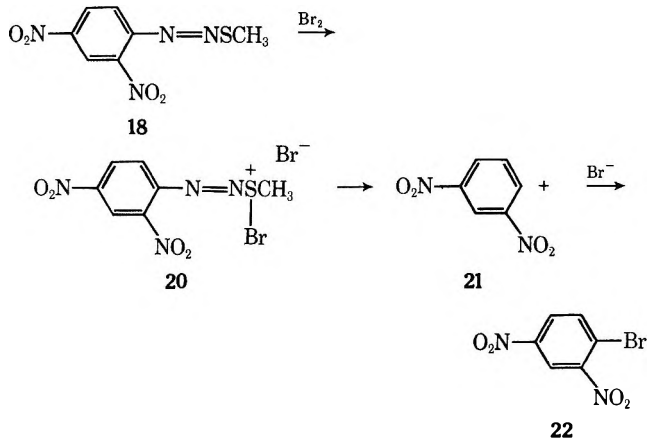
(23) K. H. Meyer, A. Irschick, and H. Schlosser, *Ber.*, **47**, 1741 (1913).

(24) J. C. Brunton and H. Suscheitzky, *J. Chem. Soc.*, 1035 (1955).

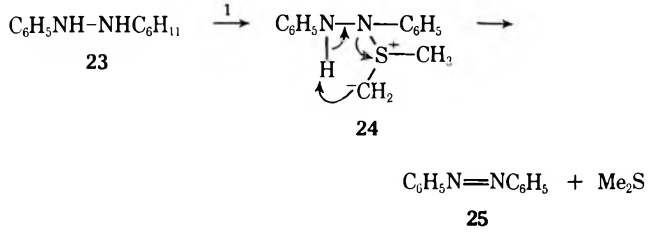
(25) J. B. Jones and D. C. Wigfield, *Can. J. Chem.*, **44**, 2517 (1966).

(26) H. W. Talen, *Recl. Trav. Chim. Pays-Bas*, **47**, 782 (1928).

(27) A. G. Kekule, *Justus Liebigs Ann. Chem.*, **137**, 167 (1866).



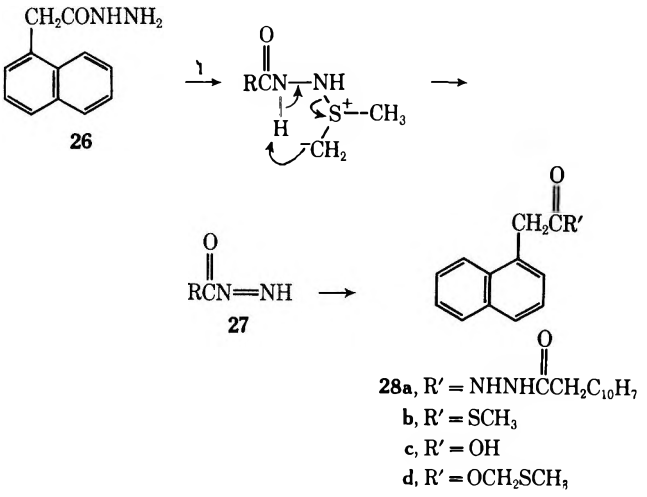
and DCC to give crystalline azobenzene (**25**) which was isolated in 94% yield. The same reaction using DMSO and phosphorus pentoxide gave **25** in 64% yield and in this case also produced some dark-colored, unidentified by-products. Formation of azobenzene presumably involves intramolecular proton abstraction and collapse of the initial sulfonium ylide **24**.



The reaction of 1-naphthylacetylhydrazide (**26**) with DMSO and phosphorus pentoxide was accompanied by nitrogen evolution and led to the isolation of four products. These were identified as *N*,*N*′-bis(1-naphthylacetyl)hydrazine (**28a**, 5%), methyl 1-naphthylthiolacetate (**28b**, 26%), 1-naphthylacetic acid (**28c**, 28%), and methylthiomethyl 1-naphthylacetate (**28d**, 2%). The formation of all of these compounds could be explained by a pathway involving initial oxidation of **26** to the acyldiimide **27**. Subsequent acid-catalyzed reactions of the latter with the available nucleophiles **26**, methyl mercaptan, phosphoric acid, and DMSO would then lead to the observed products (**28a–d**), the latter *via* the mechanism described earlier for reactions of carboxylic acids with DMSO and DCC. These reactions could, of course, all proceed *via* initial acid-catalyzed heterolysis to the acyl cation rather than being truly concerted. Previous work by Cohen and Nicholson[28] and by Kelly[29] has demonstrated both the oxidation of *N*-acyl-*N*′-arylhydrazines with manganese dioxide or lead tetraacetate to the corresponding diimides and nucleophilic decomposition of the latter to acyl derivatives.

The reaction of **26** with DMSO and DCC led predominantly to the diacylhydrazine **28a** and was complicated by the extreme insolubility of this compound, which crystallized from the reaction mixture with the dicyclohexylurea. By using diisopropylcarbodiimide in place of DCC, the much more soluble urea by-product could be readily removed with hot methanol, leaving pure **28a** in 58% yield.

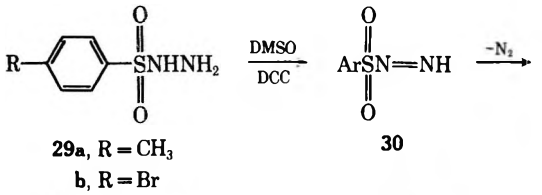
(28) S. G. Cohen and J. Nicholson, *J. Org. Chem.*, **30**, 1162 (1965).
(29) (a) R. B. Kelly, *ibid.*, **28**, 453 (1963); (b) *ibid.*, **29**, 1273 (1964).



The reaction of sulfonyl hydrazides took a somewhat different course. Treatment of *p*-toluenesulfonyl hydrazide (**29a**) with DMSO, DCC, and anhydrous phosphoric acid led to immediate evolution of nitrogen and the formation of several products. The aqueous extracts were shown by paper chromatography, paper electrophoresis, and ultraviolet spectra to contain roughly 70% of *p*-toluenesulfonic acid (**34a**). The organic phase contained two major products, both of which were isolated in crystalline form by preparative tlc. The less polar product (24%) was shown to be the known *p*-tolyl *p*-toluenethiolsulfonate (**33a**)[30] while the other substance (7%) was an adduct of toluenesulfinic acid and DCC for which we tentatively suggest the structure **35**. This structure is supported by the similarity of its intense infrared absorption band at 1685 cm^{-1} to that in *N*-acylureas and by the ready decomposition of **35** to, *inter alia*, **33a**, upon heating. The presence of a peak at *m/e* 139 ($CH_3C_6H_4SO$) in its mass spectrum also suggests a sulfinyl structure but is not compelling.

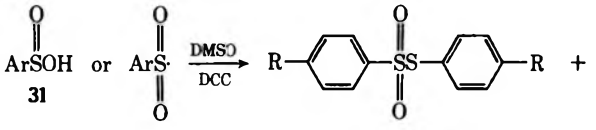
Thiolsulfonates and sulfonic acids are known to result from the disproportionation of sulfinic acids[31] or of sulfonyl radicals.[32] We suggest that the present reaction leads (as in **26** → **27**) initially to the sulfonyldiimide **30**, which then loses nitrogen to form the sulfinic acid **31**. Indeed, reaction of *p*-toluenesulfinic acid (**31**)[31] with DMSO, DCC, and phosphoric acid leads to the same two products, **33a** and **35**, in modest yield although in this case, the urea adduct preponderates. Since no **33a** is formed upon short storage of the sulfinic acid **31** in DMSO either alone or in the presence of anhydrous phosphoric acid, we must conclude that, if the free sulfinic acid is an intermediate in the DMSO–DCC reaction, it must undergo further activation prior to disproportionation. Collapse of the diimide **30** to a sulfonyl radical **32** could also explain the formation of **33** and *p*-toluenesulfonic acid.[32] *p*-Bromobenzenesulfonylhydrazide (**39b**) appears to react in a similar way with DMSO–DCC, and the thiolsulfonate **33b** and bis(4-bromophenyl)disulfide were isolated in crystalline form.

(30) P. Karrer, W. Wehrli, E. Biedermann, and M. Vedova, *Helv. Chim. Acta*, **11**, 233 (1928).
(31) J. L. Kice, G. Guaraldi, and C. G. Venier, *J. Org. Chem.*, **31**, 3561 (1966), and references cited therein.
(32) C. M. M. da Silva Correa and W. A. Waters, *J. Chem. Soc. C*, 1874 (1968).



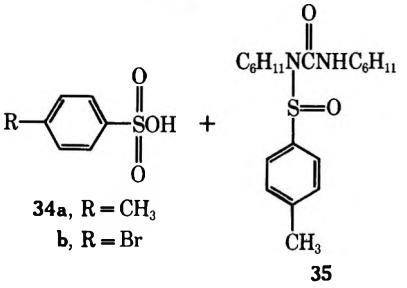
29a, R = CH_3
b, R = Br

30



31 32

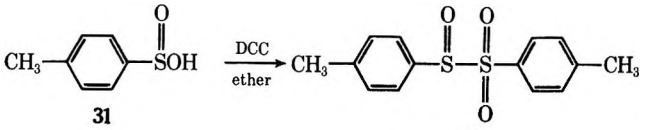
33a, R = CH_3
b, R = Br



34a, R = CH_3
b, R = Br

35

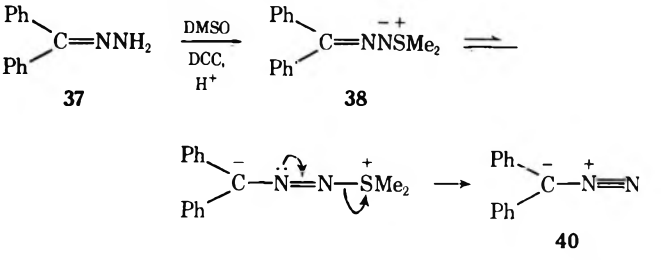
The reaction of **31** with DCC in ether or methylene chloride gave only small amounts of **33a** and **35**, the major product being *p*-toluenesulfinyl *p*-tolylsulfone (**36**), which was isolated in 82% yield. This compound was previously obtained from reaction of **31** with acetic anhydride and sulfuric acid and was at that time considered to be the symmetrical sulfinic anhydride.[33] The structure of **36** was clarified by Bredereck, *et al.*,[34] who provided an alternative synthesis. The exact mechanism of the formation of **36** from **31** with DCC is not clear, as is the question of whether **36** could be an intermediate in the formation of **33a**.[31]



31 36

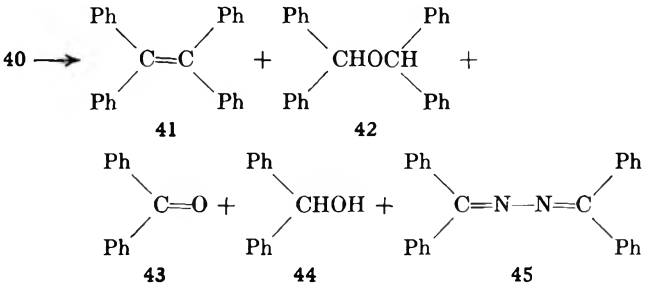
The reaction of benzophenone hydrazone (**37**) with DMSO and DCC led to rapid nitrogen evolution and formation of a dark red color. Preparative tlc of the reaction mixture led to the isolation of tetraphenylethylene (**41**, 5%), dibenzhydryl ether (**42**, 12%), benzophenone (**43**, 24%), and benzhydrol (**44**, 19%), the latter as its acetate, presumably due to transesterification with ethyl acetate during the work-up. These products can all arise from diphenyldiazomethane (**40**) and, indeed, immediate extraction of a reaction mixture with hexane removed a red substance with an ultraviolet spectrum identical with that of authentic **40**.[35] Similar treatment of crystalline **40** with DMSO, DCC, and anhydrous phosphoric acid gave **41** (16%), **42** (17%), **43** (15%), **44** (16%), and in addition a 6% yield of benzophenoneazine (**45**) which was probably also formed from **37** but not isolated.

Formation of diphenyldiazomethane from **37** can be rationalized by the scheme below (**37** → **40**) with initial formation of the iminosulfilimine intermediate **38** being similar to what was previously described for the reactions of amides.[1,7]



37 38

40



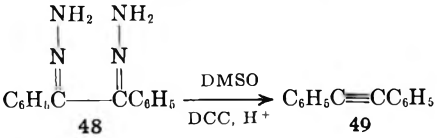
41 42

43 44 45

The reaction of **37** with DMSO and phosphorus pentoxide was somewhat different since neither **41** nor **42** was isolated. The major product was benzhydrol (**44**) in 42% yield, and in addition, benzophenone (**48**), the azine **45**, and benzhydryl methyl sulfide (**47**) were isolated in yields of 19, 9, and 10%, respectively. From the color of the reaction mixture, **40** was probably once again formed but due to the much more acidic nature of the medium, this compound would decompose to the benzhydryl cation. Reaction of the latter with DMSO would give the oxysulfonium salt **46**, which would lead to **43** and **44**, while reaction with methyl mercaptan would form the sulfide **47**.

46 47

The only other hydrazone examined was benzil dihydrazone (**48**), which reacted with vigorous evolution of nitrogen. In addition of 15% of benzil, the only pure product isolated was diphenylacetylene (**49**) which was obtained in 21% yield. Conversion of **48** to **49** has previously been achieved using oxidants such as mercuric oxide.[36] In the present case, the reaction clearly involves diazo intermediates formed as above, and a variety of tentative mechanisms can be drawn. All are fairly complex, however, and in the absence of any compelling evidence in favor of one or the other, we prefer not to make any precise suggestion.

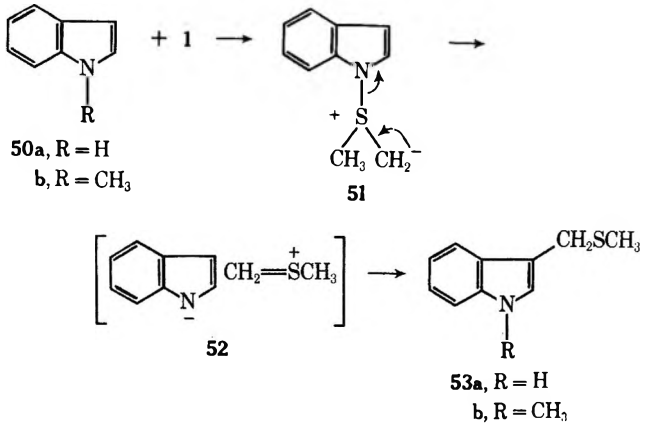


48 49

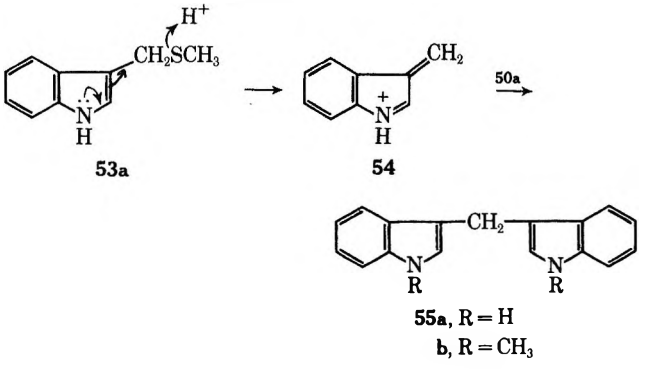
Finally, we mention the results of a few experiments with indole derivatives. Thus, it was found that indole (**50a**) itself reacts very slowly with DMSO and

(33) E. Knoevenagel and L. Pollack, *Ber.*, **41**, 3323 (1908).
(34) H. Bredereck, A. Wagner, H. Beck, and R.-J. Klein, *ibid.*, **93**, 2736 (1960).
(35) J. B. Miller, *J. Org. Chem.*, **24**, 560 (1959).
(36) A. C. Cope, D. S. Smith, and R. J. Cotter, "Organic Syntheses," Collect. Vol. IV, N. Rabjohn, Ed., Wiley, New York, N. Y., 1963, p 377.

DCC under the usual conditions. Even after 9 days at room temperature 33% of unreacted **50a** was recovered and two new products were isolated in modest yield. These proved to be 3-(methylthiomethyl)-indole (**53a**, 10%) and 3,3′-bisindolylmethane (**55a**, 6%), the latter being a known coumpound[37] and the former being readily identified by its nmr spectrum.[38] The spectrum of **53a** clearly shows that C_2–H is coupled only to NH, thus confirming the point of alkylation as C_3. Compound **53a** would appear most likely to arise through condensation of **50a** with the methylmethylene sulfonium ion (**52**). The latter ion has been encountered many times in our work and is considered to generally arise by dissociation of any ylide such as **51**. Recombination of the ion pair would be expected to lead to alkylation at C_3.



The dimer **55a** has previously been prepared both by condensation of indole with formaldehyde and zinc chloride and by treatment of 3-(hydroxymethyl)- or 3-(ethoxymethyl)indole with base.[37] In the present reaction it could arise by acid-catalyzed decomposition of **53a** to the ion **54**, which then couples with indole. To test this a mixture of **50a** and **53a** was treated with anhydrous phosphoric acid in DMSO and it was shown by tlc and vpc that **55a** was formed in 10% yield.



Treatment of *N*-methylindole (**50b**)[39] with DMSO and DCC also led to a very slow reaction from which only the dimer **55b** (8%) could be isolated in addition to unreacted **50b**. The absence of the methylthiomethyl derivative **53b** is to be expected if the formation **53a** is indeed *via* dissociation of the ylide **51**, and we have previously provided evidence that the ion **52** does not arise to any extent by decomposition of of ylides related to **1**.[4b] The formation of **55b** may be a consequence of condensation of **50b** with formaldehyde resulting from slow decomposition of DMSO.

From this and several previous papers[1,7] it is clear that many types of nitrogenous functional groups undergo interesting acid-catalyzed reactions with DMSO and DCC. In a future publication the reactions of some sulfur-containing groups will be considered.[40]

Experimental Section

General Methods.—The general methods employed are similar to those described previously.[1] Unless otherwise stated, mass spectra were obtained at an ionizing voltage of 70 eV. We are particularly indebted to Dr. M. L. Maddox and Mrs. J. Nelson and to Dr. L. Tokes for their continuous help in obtaining the reported nmr and mass spectral data.

***S,S*-Dimethyl-*N*-*p*-nitrophenylsulfilimine (7a).**—A solution of *p*-nitroaniline (1.39 g, 10 mmol), DCC (6.18 g, 30 mmol), and anhydrous phosphoric acid (15 mmol) in DMSO (10 ml) and benzene (10 ml) was kept overnight at room temperature. Ether (100 ml) and water (100 ml) were added and the mixture was filtered. The ether phase was extracted three times with water and the combined aqueous extracts were adjusted to pH 12 with sodium hydroxide giving yellow needles of **7a** (0.90 g).

The mother liquors were extracted three times with methylene chloride and the organic phase was dried ($MgSO_4$) and evaporated, leaving 1.43 g of needles. This was combined with the first crystalline product and recrystallized from methylene chloride–ether giving 1.63 g (82%) of **7a**: mp 163–165° (lit.[12b] mp 148–151°); λ_{max}^{MeOH} 234 mμ (ε 6200), 386 (16,700); nmr ($CDCl_3$) 2.72 (s, 6, SMe), 6.72 and 8.00 ppm (d, 2, J = 9 Hz, Ar); mass spectrum m/e 198 (M^+), 183 ($M - CH_3$), 153, 138 ($NO_2C_6H_4NH_2$), 62 (Me_2S), 61 ($CH_3S^+{=}CH_2$).

Anal. Calcd for $C_8H_{10}N_2O_2S$: C, 48.48; H, 5.09; N, 14.14; S, 16.17. Found: C, 48.33; H, 5.08; H, 14.21; S, 16.07.

1,3,5-Tris(4-nitrophenyl)hexahydro-*s*-triazine (8).—Phosphorus pentoxide (3.6 g) was added, with cooling, to anhydrous DMSO (15 ml). After 15 min *p*-nitroaniline (2.76 g, 20 mmol) was added, giving a clear solution. The solution was stirred for 48 hr during which time a solid material separated. The mixture was diluted with methanol and the chromatographically homogeneous product (**8**, 1.43 g, 48%) was collected. After recrystallization from pyridine this material turned orange above 250° and melted with decomposition at 286–287°: $\lambda_{max}^{dioxane}$ 355 mμ; ir (KBr) no NH; nmr (DMSO-d_6) 5.36 (s, 2, NCH_2N), 7.23 and 8.09 ppm (d, 2, J = 8 Hz, Ar); mass spectrum m/e 150 ($NO_2C_6H_4NCH_2$), 120 (m/e 150 − NO).

Anal. Calcd for $C_{21}H_{18}N_6O_6$: C, 56.00; H, 4.03; N, 18.66; O, 21.30. Found: C, 56.20; H, 3.99; N, 18.49; O, 21.50.

Reaction of *o*-Nitroaniline with DMSO and Phosphorus Pentoxide.—*o*-Nitroaniline (2.76 g, 20 mmol) was added to a premixed solution of phosphorus pentoxide (3.6 g) in DMSO (15 ml) and the resulting solution was stirred at 23° for 3 days. The resulting precipitate was collected and washed thoroughly with methanol, giving 1.87 g of a yellow solid that was crystallized from pyridine with mp 238–240° (gas evolution). This material was identical with the polymer (**10**) prepared from *o*-nitroaniline, formaldehyde, and hydrochloric acid:[16] $\lambda_{max}^{dioxane}$ 424 mμ ($\epsilon_{1\%}$ 281), 238 (935); ir (KBr) 3390, 1635, 1570, 1525 cm^{-1}; nmr (DMSO-d_6 4.50 (br s, 2, NCH_2N), 6.93 (q, 1, J_o = 9 Hz, J_m = 2 Hz, C_6H), 7.56 (br q, 1, J_o = 9, J_m = 2 Hz, C_5H), 8.07 (d, 1, J_m = 2 Hz, C_3H).

Anal. Calcd for $(C_7H_6N_2O_2)_n$: C, 56.00; H, 4.03; N, 18.66; O, 21.31. Found: C, 56.03; H, 4.39; N, 18.83; O, 21.44.

***N,N′*-Bis(2,4-dinitrophenyl)methylenediamine (9b).**—2,4-Dinitroaniline (2.74 g, 20 mmol) was added to a premixed solution of phosphorus pentoxide (2.6 g) in DMSO (10 ml). A yellow precipitate slowly separated and the mixture was stirred for 5 days. The precipitate was filtered, thoroughly washed with DMSO and chloroform, and dried, giving 2.41 g (82%) of chromatographically homogeneous **9b** with mp 275–277° (dec with gas evolution) from pyridine: $\lambda_{max}^{dioxane}$ 260 mμ (ε 18,900), 338 (30,200); mass spectrum m/e 195 [$(NO_2)_2C_6H_3N{=}CH_2$], 183

(37) E. E. Leete and L. Marion, *Can. J. Chem.*, **31**, 775, 1195 (1953).

(38) For the nmr spectra of indole derivatives, see L. A. Cohen, J. W. Daly, H. Kny, and B. Witkop, *J. Amer. Chem. Soc.*, **82**, 2184 (1960).

(39) K. T. Potts and J. E. Saxton, *J. Chem. Soc.*, 2641 (1954).

(40) Unpublished work by J. G. Moffatt.

$[(NO_2)_2C_6H_3NH_2]$, 167 (*m/e* 183 − O), 153 (*m/e* 183 − NO), 137 (*m/e* 183 − NO_2).

Anal. Calcd for $C_{13}H_{10}N_6O_6$: C, 41.28; H, 2.66; N, 22.22; O, 33.84. Found: C, 41.33; H, 2.88; N, 22.31; O, 33.89.

***S,S*-Dimethyl-*N*-*m*-nitrophenylsulfilimine (7b).**—A solution of *m*-nitroaniline (1.39 g, 10 mmol), DCC (6.18 g, 30 mmol), and anhydrous phosphoric acid (15 mmol) in DMSO (10 ml) and benzene (10 ml) was kept at 23° for 2 hr. The mixture was diluted with ether and extracted three times with water. The aqueous extracts were made alkaline with sodium hydroxide and extracted with methylene chloride. Evaporation of the organic extracts and crystallization from carbon tetrachloride gave 1.68 g (85%) of **7b** as dark red needles with mp 100–101° (lit.[12b] mp 96–98°): λ_{max}^{MeOH} 260 mμ (ε 15,100), 394 (1200); nmr ($CDCl_3$) 2.68 (s, 6, SMe_2), 7.0–7.7 (m, 4, Ar); mass spectrum *m/e* 198 (M^+), 183 (M − CH_3), 168 (M − 2 CH_3 or M − CH_3 and NO), 136 (M − SMe_2), 122 ($NO_2C_6H_4^+$), 62 (Me_2S).

Anal. Calcd for $C_8H_{10}N_2O_2S$: C, 48.48; H, 5.09; N, 14.14; S, 16.17. Found: C, 48.29; H, 4.99; N, 14.17; S, 16.06.

***S,S*-Dimethyl-*N*-(3,5-dinitrophenyl)sulfilimine (7c).**—A reaction between 3,5-dinitroaniline (1.83 g, 10 mmol), DCC (6.18 g, 30 mmol), and anhydrous phosphoric acid (15 mmol) in DMSO (10 ml) and benzene (10 ml) for 1 hr was worked up exactly as above for **7b**. Crystallization of the crude product from chloroform–carbon tetrachloride gave **7c** (1.80 g, 74%) as orange needles with mp 168–170° unchanged on recrystallization from ethanol: λ_{max}^{MeOH} 227 mμ (ε 18,500), 260 (20,700), 350 (1600), 410 (1500); nmr (DMSO-d_6) 2.77 ppm (s, 6, SMe_2), 7.5–7.8 (m, 3, Ar); mass spectrum *m/e* 243 (M^+), 228 (M − CH_3), 62 (Me_2S).

Anal. Calcd for $C_8H_9N_3O_4S$: C, 39.51; H, 3.73; N, 17.28; S, 13.17. Found: C, 39.35; H, 3.88; N, 17.05; S, 12.95.

Reactions of *p*-Anisidine. A. With DMSO–DCC.—Anhydrous phosphoric acid (15 mmol) and DCC (6.18 g, 30 mmol) were added to a solution of *p*-anisidine (1.23 g, 10 mmol) in DMSO (10 ml) and benzene (10 ml) under argon. After 20 min the mixture was partitioned between water and ether and the water was washed with methylene chloride. The aqueous solution was made alkaline with sodium hydroxide and extracted with methylene chloride. The organic extracts were washed with water, dried, and evaporated, giving 1.76 g of a semicrystalline oil. Crystallization from ether at −15° after charcoal treatment gave 610 mg (19%) of 1,3-dicyclohexyl-2-(4-methoxyphenyl)-guanidine (**3**) as white needles with mp 142–144°:[41] λ_{max}^{MeOH} 233 mμ (ε 9400); nmr ($CDCl_3$) 0.8–2.3 (m, 20 H, cyclohexyl), 3.5 (m, 4, >CHN and NH), 3.75 (s, 3, OCH_3), 6.79 ppm (s, 4, Ar); mass spectrum *m/e* 329 (M^+), 247 (M − C_6H_{10}), 123 ($MeOC_6H_4NH_2$).

Anal. Calcd for $C_{20}H_{31}N_3O$: C, 72.90; H, 9.48; N, 12.76. Found: C, 72.81; H, 9.39; N, 12.92.

B. With DMF–DCC.—A reaction was carried out exactly as in A except that the DMSO was replaced by dimethylformamide (20 ml). After 4 hr it was worked up as above, evaporation of the extracts following basification giving 1.60 g of a chromatographically homogeneous, clear syrup that could not be crystallized. An ether solution of one half of this was treated with an excess of hydrogen chloride in dioxane, giving 0.94 g (88%) of *N*-(4-methoxyphenyl)-*N'*,*N'*-dimethylformamidinium chloride (**4**)[42] which was readily recrystallized from ethanol with mp 207–212° dec: λ_{max}^{MeOH} 265 mμ (ε 1300); nmr (D_2O) 3.27 and 3.43 (s, 3, N^+Me),[43] 3.87 (s, 3, OMe), 7.2 (m, 4, Ar), 8.25 ppm (s, 1, NCH=N^+<).

Anal. Calcd for $C_{10}H_{15}N_2OCl$: C, 55.96; H, 7.04; N, 13.05. Found: C, 55.59; H, 7.02; N, 13.02.

During attempted crystallization of the free base of **4** from aqueous methanol considerable hydrolysis occurred. Subsequent crystallization from ether gave 4-methoxyformanilide (**5**) with mp 80–81.5° (lit.[44] mp 80–81°) and in all ways identical with an authentic sample from anisidine, acetic anhydride, and formic acid:[45] λ_{max}^{MeOH} 250 mμ (ε 14,500); nmr ($CDCl_3$) 3.78 (s, 3 OCH_3), 6.7–7.6 (m, 4, Ar), 8.27 and 8.57 ppm (br s, total 1 H, CHO);[46] mass spectrum *m/e* 151 (M^+), 122 (M − CHO), 108 ($C_6H_5OCH_3$).

Reaction of 2,4-Dinitrophenylhydrazine (11). A. With DMSO–DCC.—A solution of **11** (1.98 g, 10 mmol), DCC (5.8 g, 28 mmol), and anhydrous phosphoric acid (5 mmol) in DMSO (10 ml) was kept at room temperature with occasional cooling (gas evolution) for 1 hr. The mixture was diluted with ethyl acetate and water and filtered, and the organic phase was washed three times with water. Evaporation of the dried solution followed by preparative tlc on three plates using three developments with benzene–CCl_4 (1:1) gave three major bands as well as a complex mixture on the origin. Elution of the fastest band gave 480 mg (29%) of *m*-dinitrobenzene with mp 90–91° from ethanol and identical with an authentic sample: nmr ($CDCl_3$) 7.90 (AB_2 q, 1, J = 8.5 Hz, C_5H), 8.66 (q, 2, J_o = 8.5, J_m = 2 Hz, C_4H, C_6H), 9.10 ppm (t, 1, J_m = 2 Hz, C_2H).

Elution of the middle band followed by rechromatography using CCl_4–MeOH (99:1) gave 232 mg (11%) of 2,4-dinitrophenyl methylsulfide (**19**) with mp 125–127° from ethanol (lit.[17] mp 128°): λ_{max}^{MeOH} 269 mμ (ε 5300), 332 (10,200); nmr ($CDCl_3$) 2.60 (s, 3, SMe), 7.40 (d, 1, J_o = 9 Hz, C_6H), 8.35 (q, 1, J_o = 9, J_m = 2 Hz, C_5H), 9.06 ppm (d, 1, J_m = 2 Hz, C_3H); mass spectrum *m/e* 214 (M^+), 199 (M − CH_3), 184 (M − NO), 151 (*m/e* 184 − SH), 121 (*m/e* 154 − NO).

Elution of the slowest band and crystallization from acetone gave 32 mg (2%) of 2,2',4,4'-tetranitroazobenzene: mp 223–225° (lit.[18] mp 221°); λ_{max}^{MeOH} 304 mμ (ε 18,900); mass spectrum *m/e* 362 (M^+), 195 [M − $C_6H_3(NO_2)_2$].

Anal. Calcd for $C_{12}H_6N_6O_8$: C, 39.79; H, 1.67; N, 23.20. Found: C, 39.99; H, 1.79; N, 23.17.

B. With DMSO–P_2O_5.—Phosphorus pentoxide (2.5 g) was added portionwsie to DMSO (30 ml), followed, after 20 min, by **11** (3.97 g, 15 mmol). After 16 hr at 23° the mixture was partitioned between chloroform and water and 490 mg of a highly insoluble unidentified material (polymer?) was removed by filtration. The organic phase was purified by preparative tlc on three plates using two developments with benzene–CCl_4 (3:2) giving three bands and an intractable streak near the origin. Elution of the fastest band and crystallization from methanol gave 473 mg (13%) of methylthio(2,4-dinitrophenyl)diimide (**18**) as long yellow needles with mp 107.5–108°: λ_{max}^{MeOH} 250 mμ (ε 9100), 342 (15,200); nmr ($CDCl_3$) 2.85 (s, 3, SMe), 7.60 (d, 1, J_o = 9 Hz, C_6H), 8.47 (q, 1, J_o = 9, J_m = 2 Hz, C_5H), 8.73 ppm (d, 1, J_m = 2 Hz, C_3H); mass spectrum *m/e* 242 (M^+), 195 (M − SCH_3), 75 [$C_6H_3(NO_2)_2$].

Anal. Calcd for $C_7H_6N_4O_4S$: C, 34.71; H, 2.50; N, 23.13; S, 13.24. Found: C, 34.83; H, 2.97; N, 22.90; S, 13.01.

Elution of the second band and crystallization from ethanol gave 126 mg (5%) of *m*-dinitrobenzene (mp 90–91°) while elution of the slower band and crystallization from methanol gave 989 mg (31%) of **19** with mp 125–127°.

C. With DMSO–P_2O_5 in the Presence of 1-Naphthol.—Phosphorus pentoxide (3.2 g) was slowly added to DMSO (20 ml) followed by 1-naphthol (4.32 g, 30 mmol) and 2,4-dinitrophenylhydrazine (2.97 g, 15 mmol). A crystalline product separated and after 2.5 hr the mixture was diluted with methanol and filtered, giving 1.95 g (39%) of 4-(2,4-dinitrophenylazo)-1-naphthol, which was recrystallized from pyridine with mp 276–278° (lit.[23] mp 278°): $\lambda_{max}^{OH^-}$ 245 mμ (sh, ε 15,100), 314 (10,000).

D. With DMSO–P_2O_5 and Dimethyl Disulfide.—Phosphorus pentoxide (16 g) was added slowly at 0° to a mixture of DMSO (75 ml) and dimethyl disulfide (20 ml). 2,4-Dinitrophenylhydrazine (15 g) was then added and the mixture was stirred at −10° for 1 hr, at 0° for 2 hr, and at 23° for 1 hr. The red mixture was then partitioned between chloroform and water and filtered, and the organic phase was washed with aqueous bicarbonate, dried, and evaporated. The residue was applied to a 6 × 50 cm column of silicic acid and eluted with benzene–CCl_4 (1:1), giving 7.8 g (43%) of crystalline **18** which was recrystallized from methanol with mp 107–108°.

E. With DMSO–DCC–Dimethyl Disulfide.—Anhydrous phosphoric acid (6 mmol) was added to a solution of **11** (1.98 g, 10 mmol), DCC (5.89, 28 mmol), and dimethyl disulfide (5 ml) in DMSO (10 ml). After 16 hr at 2°, the mixture was worked up as in A, giving 493 mg (20%) of the diazosulfide **18**, 179 mg (11%) of *m*-dinitrobenzene, and 682 mg (32%) of **19**.

Methylthio(2,4-dinitrophenyl)diimide (18).—2,4-Dinitrophen-

(41) The reaction was nearly quantitative by tlc but crystallization of **3** was difficult and accompanied by some decomposition.

(42) The perchlorate of **4** has been described: D. Duerr, H. Aebi, and L. Ebner, U. S. Patent 3,284,289 (1966); *Chem. Abstr.*, **66**, 28499 (1967).

(43) Magnetic nonequivalence of the methyl groups in *N,N*-dimethylformamidines has been described by J. P. Marsh and L. Goodman, *Tetrahedron Lett.*, 683 (1967).

(44) C. W. Huffman, *J. Org. Chem.*, **23**, 727 (1958).

(45) H. Susagawa and H. Shigehara, *J. Pharm. Soc. Japan*, **62**, 531 (1942).

(46) Restricted rotation in para-substituted formanilides has been noted by R. E. Carter, *Acta Chem. Scand.*, **22**, 2643 (1968).

yldiazonium fluoroborate[24] (500 mg, 1.78 mmol) was added with stirring at 0° to a solution of dimethyl disulfide (1 ml) and anhydrous phosphoric acid (4 mmol) in DMSO (3 ml). After 2 hr at 0°, the mixture was diluted with chloroform, extracted several times with water, dried, and evaporated. Preparative tlc using benzene–CCl_4 (1:1) followed by crystallization from methanol gave 121 mg (28%) of **18** identical with that above.

Thermal Decomposition of 18. A. Without Solvent.—Dry **18** (700 mg) was heated at 140° for 3 hr, during which time there was continuous gas evolution.[47] The temperature was raised to 160° for 30 min and the cooled residue was purified by preparative tlc using two developments with CCl_4–benzene (7:3), giving four bands. Elution of the fastest band gave 109 mg (16%) of unreacted **18**. The second band contained 13 mg (3%) of *m*-dinitrobenzene, while elution of the third band gave 446 mg (72%) of crystalline **19** identical with that above. Elution of the slowest band and crystallization from methanol gave 27 mg (5%) of bis(2,4-dinitrophenyl)sulfide with mp 196.5–198° (lit.[26] mp 196°); mass spectrum *m/e* 366 (M^+).

Anal. Calcd for $C_{12}H_6N_4O_8S$: C, 39.35; H, 1.65; N, 15.30; S, 8.76. Found: C, 39.31; H, 1.72; N, 15.11; S, 8.92.

B. In Dimethylformamide.—A solution of **18** (700 mg) in dimethylformamide (2 ml) was heated at 160° for 6 hr. It was then diluted with chloroform, extracted several times with water, evaporated, and purified by preparative tlc as above giving 6% of unreacted **18**, 27% of *m*-dinitrobenzene, and 25% of **19**.

Reaction of 18 with Acid and 1-Naphthol.—1-Naphthol (100 mg, 0.7 mmol) and **18** (121 mg, 0.5 mmol) were dissolved in a 3.8 *M* solution of hydrogen chloride in dioxane and kept at room temperature for 30 hr. After addition of ether (5 ml) the crystalline product was collected and washed, giving 131 mg (78%) of 4-(2,4-dinitrophenylazo)-1-naphthol, which was recrystallized from pyridine with mp 276–278° identical with that above.

Reaction of 18 with Bromine.—A 1 *M* solution of bromine in chloroform (2.3 ml) was added to an ice-cooled solution of **18** (500 mg, 2.07 mmol) in chloroform (4 ml). After nitrogen evolution had ceased, the mixture was evaporated and purified by preparative tlc using hexane–benzene (2:1). Elution of the major band gave 487 mg (96%) of crystalline 2,4-dinitrobromobenzene (**22**) with mp 72–73° after recrystallization from methanol (lit.[27] mp 72°): λ_{max}^{MeOH} 206 mμ (ε 15,300), 266 (12,100); nmr ($CDCl_3$) 8.07 (d, 1, J_o = 9 Hz, C_6H), 8.38 (q, 1, J_o = 9 Hz, J_m = 2 Hz, C_5H), 8.70 ppm (d, 1, J_m = 2 Hz, C_3H); mass spectrum *m/e* 246 and 248 (M^+).

Reaction of *p*-Toluenesulfonyl Hydrazide (29a).—Anhydrous phosphoric acid (5 mmol) was added to a solution of **29a** (1.86 g, 10 mmol) and DCC (5.8 g, 28 mmol) in DMSO (10 ml) and benzene (5 ml). Nitrogen evolution was almost immediate, and after 1 hr with periodic cooling the mixture was diluted with ethyl actate and water, filtered, washed with water, and purified by preparative tlc using CCl_4–ethyl acetate (19:1). A very fast band containing an unidentified, volatile material and two slower bands resulted. Elution of the faster band gave 326 mg (24%) of crystalline *p*-tolyl *p*-toluenethiolsulfonate (**33a**) with mp 75–78° from hexane (lit.[30] mp 76°): λ_{max}^{MeOH} 236 mμ (ε 19,800), 270 (sh, 6400); nmr 2.36 and 2.40 (s, 3, $ArCH_3$), 7.0–7.6 (m, 8, Ar); mass spectrum *m/e* 278 (M^+), 139 ($CH_3C_6H_4SO$), 123 ($CH_3C_6H_4S$).

Anal. Calcd for $C_{14}H_{14}S_2O_2$: C, 60.42; H, 5.07; S, 23.01. Found: C, 60.54; H, 5.07; S, 23.08.

Elution of the slower band gave 270 mg (7%) of crystalline **35** that was recrystallized from hexane with mp 89–91° (sensitive to rate of heating) with partial resolidification: λ_{max}^{MeOH} 222 mμ (ε 9700), 239 (9600); ν_{max} (KBr) 3340, 1685, 1540 cm^{-1}; nmr ($CDCl_3$) 0.9–2.2 (m, 20, cyclohexyl), 2.40 (s, 3, $ArCH_3$), 3.3 and 4.1 (m, 1, >CHN), 7.26 and 7.52 (d, 2, *J* = 8 Hz, Ar); mass spectrum *m/e* 362 (M^+), 280 (M − C_6H_{10}), 220, 139 (MeC_6H_4SO), 98 ($C_6H_{11}NH$).

Anal. Calcd for $C_{20}H_{30}N_2O_2S$: C, 66.27; H, 8.34; N, 7.73. Found: C, 66.21; H, 8.27; N, 7.74.

The aqueous extracts were shown by paper chromatography and electrophoresis to contain roughly 7 mmol (70%) of *p*-toluenesulfonic acid based upon ultraviolet spectra.

***p*-Toluenesulfinyl *p*-Tolyl Sulfone (36).**—DCC (1.03 g, 5 mmol) was added to a solution of *p*-toluenesulfinic acid (1.56 g, 10 mmol)[31] in methylene chloride (25 ml). After 10 min the mixture was filtered, giving 0.93 g of dicyclohexylurea, and the filtrate was concentrated to about 5 ml. Gradual addition of hexane (10 ml) led to crystallization of 1.21 g (82%) of **36** with mp 83–85°, unchanged upon recrystallization (lit.mp 75°,[33] 76°,[48] 87°[34]): ir identical with that reported;[34] λ_{max}^{MeOH} 222 mμ (ε 19,800), 244 (8700) and changing with time; nmr ($CDCl_3$) 2.47 (s, 6, $ArCH_3$), 7.2–7.7 (m, 8, Ar).

Anal. Calcd for $C_{14}H_{14}S_2O_3$: C, 57.14; H, 4.80. Found: C, 57.19; H, 4.78.

Reaction of *p*-Bromobenzenesulfonyl Hydrazide (29b).—A reaction between **29b** (2.51 g, 10 mmol), DCC (5.8 g, 28 mmol), and anhydrous phosphoric acid (5 mmol) in DMSO (10 ml) and benzene (10 ml) was kept for 16 hr with cooling during the early stages. It was worked up in the usual way with ethyl acetate and purified by preparative tlc using CCl_4–benzene (4:1). Elution of a very fast band and crystallization from methanol gave 67 mg (2%) of bis(4-bromophenyl)disulfide with mp 90.5–92° (lit.[49] mp 93–94°): nmr ($CDCl_3$) 7.2–7.5 ppm (m, 8, Ar); mass spectrum *m/e* 372, 374, 376 (M^+), 295, 297 (M − Br), 216 (M − 2Br), 187, 189 (BrC_6H_4S), Elution of the slower band followed by crystallization from ether–hexane gave 235 mg (12%) of 4-bromophenyl 4-bromobenzenethiolsulfonate (**33b**) with mp 160–161°: λ_{max}^{MeOH} 243 mμ (ε 23,100); nmr ($CDCl_3$) 7.1–7.8 (m, 8, Ar).

Anal. Calcd for $C_{12}H_8Br_2O_2S_2$: C, 35.12; H, 1.96; S, 15.70. Found: C, 35.46; H, 1.73; S, 15.69.

Reaction of Hydrazobenzene (23). A. With DMSO–DCC.—A solution of **23** (1.84 g, 10 mmol), DCC (5.8 g, 28 mmol), and anhydrous phosphoric acid was allowed to react in DMSO (5 ml) and benzene (5 ml) for 4 hr and then worked up with ethyl acetate. Preparative tlc using two developments with CCl_4–$CHCl_3$ (4:1) gave essentially a single product that was eluted giving 1.72 g (94%) of crystalline azobenzene (**25**) with mp 68–69° and λ_{max}^{MeOH} 316 mμ (ε 17,700), 229 (13,700), both identical with those of an authentic sample.

B. With DMSO–P_2O_5.—Hydrazobenzene (2.76 g) was added to a mixture of phosphorus pentoxide (3 g) in DMSO (15 ml) and stirred for 1 hr. The mixture was worked up with ether, giving some dark-colored, insoluble material. Preparative tlc as above gave 1.75 g (64%) of crystalline azobenzene.

Reaction of 1-Naphthylacetyl Hydrazide (26). A. With DMSO–P_2O_5.—1-Naphthylacetylhydrazide (3.0 g, 15 mmol) was added with stirring and periodic cooling to a solution of phosphorus pentoxide (2.5 g) in DMSO (20 ml). After 1 hr the mixture was diluted with chloroform and extracted three times with water with removal of 145 mg (5%) of crystalline *N,N'*-bis(1-naphthylacetyl)hydrazine (**28a**) of mp 290–292° dec, unchanged upon recrystallization from dimethylformamide–methanol: nmr (DMSO-d_6) 4.00 (s, 4, CH_2CO), 7.4–8.3 (m, 14, Ar), 10.25 ppm (s, 2, NH); mass spectrum *m/e* 368 (M^+), 168 ($C_{10}H_7CH{=}C{=}O$) 141 ($C_{10}H_7CH_2^+$).

Anal. Calcd for $C_{24}H_{20}N_2O_2$: C, 78.24; H, 5.47; N, 7.61. Found: C, 78.03; H, 5.74; N, 7.65.

Extraction of the chloroform solution with aqueous bicarbonate followed by acidification gave 783 mg (28%) of crystalline 1-naphthylacetic acid (**28c**) of mp 130–132° and identical with an authentic sample. Preparative tlc of the dried organic phase using CCl_4–acetone (19:1) gave two major bands. Elution of the faster band and short path distillation [bath temperature 90° (0.1 mm)][50] gave 853 mg (26%) of methyl 1-naphthylthioacetate (**28b**) as an oil: λ_{max}^{MeOH} 222 mμ (ε 77,000), 284 (7500); nmr ($CDCl_3$) 2.17 ppm (s, 3, SCH_3), 4.23 (s, 2, CH_2CO), 7.3–8.2 (m, 7, Ar); mass spectrum *m/e* 216 (M^+), 141 ($C_{10}H_7CH_2^+$).

Anal. Calcd for $C_{13}H_{12}OS$: C, 72.18; H, 5.59; (S, 14.83. Found: C, 71.73; H, 5.51; S, 14.76.

Elution of the slower band gave 81 mg (2%) of methylthiomethyl 1-naphthylacetate (**28d**), which could be distilled in a short path apparatus [bath temperature 95° (0.1 mm)]: nmr ($CDCl_3$) 1.96 (s, 3, SCH_3), 4.00 (s, 2, $ArCH_2CO$), 5.05 (s, 2, OCH_2S), 7.3–8.2 ppm (m, 7, Ar); mass spectrum *m/e* 246 (M^+), 141 ($C_{10}H_7CH_2^+$), 61 ($CH_3S^+{=}CH_2$). An acceptable elemental analysis was not obtained. Rechromatography of a band on the origin gave a complex mixture that was not examined further.

B. With DMSO–Diisopropylcarbodiimide.—Anhydrous phosphoric acid (2.5 mmol) was added to a solution of **26** (1.0 g, 5 mmol) and diisopropylcarbodiimide (1.89 g, 15 mmol) in DMSO (5 ml). Gas evolution and separation of crystals started after a few minutes and after 1 hr the mixture was diluted with methanol and filtered. The crystalline product was extracted twice with

(47) A sample heated directly to 150° decomposed quite violently.

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hot methanol, leaving pure **24a** (0.52 g, 58%) identical with that above. The other products were not examined.

Reaction of Benzophenone Hydrazone (37). A. With DMSO–DCC.—The reaction of **37** (1.96 g, 10 mmol), DCC (6.18 g, 30 mmol), and anhydrous phosphoric acid (5 mmol) in DMSO (10 ml) and benzene (5 ml) led to rapid gas evolution and became a dark red color.[51] After 24 hr the mixture was worked up in the usual way using ethyl acetate and the organic phase was separated into three major and several minor bands by preparative tlc using CCl_4–benzene (4:1). Elution of the fastest band and crystallization from hexane gave 86 mg (5%) of tetraphenylethylene (**41**) with mp 222–224° (lit.[52] mp 223–224°): λ_{max}^{MeOH} 238 mμ (ε 13,100), 380 (7800); nmr ($CDCl_3$) 7.05 ppm (s, 20, Ar); mass spectrum *m/e* 332 (M^+), 255 ($M - C_6H_6$).

Anal. Calcd for $C_{26}H_{20}$: C, 93.94; H, 6.06. Found: C, 94.05; H, 6.02.

Elution of the second band and crystallization from hexane gave 204 mg (12%) of dibenzhydryl ether (**42**) of mp 107–108.5° (lit.[53] mp 109°): λ_{max}^{MeOH} 253 mμ (ε 770), 259 (960), 265 (720); nmr ($CDCl_3$) 5.42 (s, 2, Ar_2CHO), 7.30 ppm (s, 20, Ar); mass spectrum *m/e* 350 (M^+), 272 ($M - C_6H_6$), 183 (Ar_2CHO^+), 167 (Ar_2CH^+), 152.

Anal. Calcd for $C_{26}H_{22}O$: C, 89.11; H, 6.33. Found: C, 88.97; H, 6.15.

Elution of the major slow spot and short path distillation [bath temperature 105° (0.07 mm)] gave 860 mg (~43%) of a colorless oil that could not be further separated by tlc in several solvents but was shown by vpc (5-ft column of NPGS on Gas-Chrom Q[54] at 150°) and nmr to be a 3:2 mixture of benzophenone and benzhydrol acetate, both being compared with authentic samples.

B. With DMSO–P_2O_5.—Phosphorus pentoxide (2.5 g) was carefully added to DMSO (20 ml) and after 20 min **37** (2.94 g, 15 mmol) was added portionwise with stirring. The mixture, which evolved nitrogen, was kept at 23° for 3 hr, diluted with chloroform, and washed with aqueous bicarbonate and water. The dried and evaporated organic phase was examined by quantitative vpc using a 5-ft column of NPGS on Gas-Chrom Q[54] at 150° which showed the two major products to be benzhydrol (42%) and benzophenone (19%). Preparative tlc using CCl_4–benzene (4:1) separated these compound as well as several other bands. Elution of the fastest band followed by rechromatography using hexane–CCl_4 (7:3) and short path distillation [bath temperature 85° (0.2 min)] gave 268 mg of benzhydryl methylsulfide (**47**) of mp 30–32° (lit.[55] mp 33°): λ_{max}^{MeOH} 248 mμ (sh, ε 1200), 260 (sh, 950); nmr ($CDCl_3$) 1.99 (s, 3, SMe), 5.10 (s, 1, Ar_2CHS), 7.2–7.7 ppm (m, 10, Ar); mass spectrum *m/e* 214 (M^+), 167 ($M - SCH_3$), 165, 152.

Anal. Calcd for $C_{14}H_{14}S$: C, 78.45; H, 6.58; S, 14.96. Found: C, 78.77; H, 6.60; S, 14.70.

The band which consisted mainly of benzophenone was rechromatographed using CCl_4–acetone (9:1) which barely resolved a faster moving substance. Crystallization of this material from hexane–ethyl acetate gave 232 mg (9%) of benzophenone azine (**45**) with mp 163–164° (lit.[56] mp 164°) that was identical with an authentic sample.

Reaction of Diphenyldiazomethane (40).—A solution of freshly prepared **40** (1.94 g, 10 mmol),[35] DCC (1.5 g), and anhydrous phosphoric acid (5 mmol) in DMSO (5 ml) and benzene (5 ml) was kept at room temperature for 24 hr. The mixture was worked up in the usual way with ethyl acetate and the organic phase was separated into five compounds by preparative tlc on three plates using carbon tetrachloride. Elution of the bands and purification as described above gave tetraphenylethylene, 266 mg (16%), mp 223–225°; dibenzhydryl ether, 301 mg (17%), mp 107–109°; benzophenone, 277 mg (15%); benzophenone azine, 107 mg (6%), mp 163–164°; and benzhydrol, 293 mg (16%), mp 66–68°.

Reaction of Benzil Dihydrazone (48).—Anhydrous phosphoric acid (20 mmol) was added to a stirred, ice-cooled solution of **48** (2.38 g, 10 mmol) and DCC (8.5 g, 41 mmol) in DMSO (5 ml) and benzene (10 ml). The temperature was slowly raised (15–20°) until a controlled evolution of nitrogen resulted. The mixture was finally kept at room temperature for 3 hr and then worked up in the usual way using ethyl acetate. The organic phase was purified by preparative tlc on three plates using benzene–chloroform (85:15). Elution of the fastest band and crystallization from ethanol gave 376 mg (21%) of diphenylacetylene (**49**) with mp 61–62° (lit.[36] mp 60–61°) that was identical (ir, tlc, and melting point) with an authentic sample. Elution of the second band and crystallization from hexane gave 318 mg (15%) of benzil with mp 96–97° and identical with an authentic sample. Elution of a band near the origin gave a complex mixture of products that was not studied further.

Reaction of Indole (50a).—A solution of anhydrous orthophosphoric acid in DMSO (2 ml of 5 *M*, 10 mmol) was added to a solution of indole (2.34 g, 20 mmol) and DCC (11.6 g, 56 mmol) in a mixture of DMSO (5 ml) and benzene (15 ml). The mixture was kept at 23° for 9 days and then diluted with ethyl acetate, and excess DCC was destroyed by addition of a solution of oxalic acid (5.0 g, 40 mmol) in methanol. After 30 min the mixture was filtered, made alkaline with sodium hydroxide, extracted three times with water, dried ($MgSO_4$), and evaporated to dryness. The residue was purified by preparative tlc using two developments with hexane–benzene (1:1), giving unreacted **50a** (770 mg, 33%) and two slower bands. Elution of the faster of these gave 350 mg (10%) of 3-(methylthiomethyl)indole (**53a**) with mp 90–91° from benzene–hexane: λ_{max}^{MeOH} 221 mμ (ε 34,300), 274 (5600), 281 (6000), 289 (5100); nmr ($CDCl_3$) 1.95 (s, 3, SCH_3), 3.83 (s, 2, In CH_2S), 6.85 (d, 1, J = 2 Hz, C_2H), 7.2 (m, 3, Ar), 7.7 ppm (m, 2, NH and C_7H); mass spectrum *m/e* 177 (M^+), 130 ($M - SCH_3$).

Anal. Calcd for $C_{10}H_{11}NS$: C, 67.75; H, 6.26; N, 7.90. Found: C, 67.82; H, 6.21; N, 7.96.

Elution of the slower band and crystallization from benzene–hexane gave 158 mg (6%) of 3,3′-bisindolylmethane with mp 163–165° (lit.[37] mp 164–165°): λ_{max}^{MeOH} 226 mμ (ε 60,300), 276 (9900), 284 (10,800), 292 (9500); nmr ($CDCl_3$) 4.22 (d, s, 2, $J_{allylic}$ = 1 Hz, CH_2), 6.86 (br d, 2, J = 2 Hz, C_2H and $C_{2'}H$), 7.0–7.35 (m, 6, Ar), 7.58 (q, 2, J_o = 7 Hz, J_m = 2 Hz, C_7H and $C_{7'}H$), 7.78 ppm (br s, 2, NH); mass spectrum *m/e* 246 (M^+), 245 ($M - H$), 218 (*m/e* 245 − HCN), 217 (*m/e* 218 − H).

In a separate experiment a solution of **53a** (29 mg), indole (50 mg), and anhydrous phosphoric acid (1 mmol) in DMSO (0.25 ml) was kept at 23° for 4 days. After neutralization with sodium hydroxide the mixture was diluted with ethyl acetate, extracted three times with water, dried, and evaporated. The presence of a roughly 10% yield of **55a** was shown by both tlc using chloroform–hexane (7:3) and vpc using a silicone oil column at 220°.

3,3′-Bis(*N*-methylindolyl)methane (55b).—A solution of *N*-methylindole (2.62 g, 20 mmol),[39] DCC (11.6 g, 56 mmol), and anhydrous phosphoric acid (11 mmol) in anhydrous DMSO (10 ml) and benzene (10 ml) was kept at 23° for 6 days. The reaction was worked up as described above for indole and purified by preparative tlc on three plates using benzene–hexane (7:13). The major band was unreacted (**50b**) while elution of the slower band gave 0.5 g of a semicrystalline yellow oil that was distilled in a Kugelrohr apparatus.[50] Crystallization from ethanol gave 212 mg (8%) of **55b** with mp 108–110°: λ_{max}^{MeOH} 228 mμ (ε 12,700), 290 (br, 2100); nmr ($CDCl_3$) 3.30 (s, 6, NMe), 4.15 (s, 2, CH_2), 6.58 (s, 2, C_2H and $C_{2'}H$), 7.1 (m, 6, Ar), 7.57 (q, 2, J_o = 7, J_m = 2 Hz, C_7H and $C_{7'}H$); mass spectrum *m/e* 274 (M^+), 273 ($M - H$), 259 ($M - CH_3$), 144 ($M^+ - N$-Me-indole).

Anal. Calcd for $C_{19}H_{18}N_2$: C, 83.18; H, 6.61; N, 10.21. Found: C, 83.25; H, 6.82; N, 9.94.

Registry No.—DMSO, 67-68-5; DCC, 538-75-0; **3**, 31896-55-6; **4**, 1202-63-7; **7a**, 31896-57-8; **7b**, 31899-31-7; **7c**, 31896-59-0; **8**, 7507-66-6; **9b**, 31896-61-4; **10**, 31872-13-6; **18**, 31899-35-1; **19**, 2363-23-7; **22**, 584-48-5; **25**, 103-33-3; **28a**, 31896-65-8; **28b**, 31896-66-9; **28d**, 31896-67-0; **33a**, 2943-42-2; **33b**, 3347-03-3; **35**, 31896-70-5; **36**, 788-86-3; **41**, 632-51-9; **42**, 574-42-5; **44**, 91-01-0; **45**, 983-79-9; **47**, 15733-08-1; **53a**, 31899-46-4; **55a**, 1968-05-4; **55b**, 31896-75-0; *m*-dinitrobenzene, 99-65-0; 2,2′,4,4′-tetranitroazobenzene, 5267-25-4; 4-(2,4-dinitrophenylazo)-1-naphthol, 3468-62-0; bis(2,4-dinitrophenyl) sulfide, 2253-67-0; bis(4-bromophenyl) disulfide, 5335-84-2.

(51) In a separated reaction omitting the benzene, the red material was immediately extracted into hexane and showed λ_{max}^{hexane} 524 mμ, identical with that of an authentic sample of diphenyldiazomethane.[35]

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Hydrolysis of Formanilides in Alkaline Solutions

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Received April 14, 1971

The rates of alkaline hydrolysis of several meta- and para-substituted formanilides are nearly independent of the nature of the substituent. pH–reaction rate profiles and entropies of activation are consistent with a mechanism involving rate-limiting general acid–general base catalyzed elimination of arylamine from the tetrahedral adduct of hydroxide ion and the anilide. *p*-Nitro- and *p*-cyanoformanilides, which are partially dissociated to unreactive conjugate bases at high pH, are anomalously reactive toward alkaline hydrolysis. The enhanced reactivity of these compounds is attributed to their hydrolysis by a mechanism involving dissociation of a dinegatively charged tetrahedral intermediate into formate ion and arylamide ion. *p*-Nitroacetanilide and *N*-methyl-*p*-nitroformanilide are also anomalously reactive, probably for the same reason. Carbonyl-^{18}O isotope exchange experiments and pH–rate profiles reveal that *p*-nitroacetanilide hydrolyzes by two processes, one first order in hydroxide ion and the other second order in hydroxide ion. The kinetics of hydrolysis of several *N*-methylformanilides suggest that these reactions are mechanistically similar to hydrolyses of the corresponding formanilides.

Prior to 1950, little was known about the kinetics of carboxamide saponification; Reid[2,3] had investigated the effects of aryl substituents on the rate of alkaline hydrolysis of benzamides, and Crocker[4] and Calvet[5] had studied the influence of acyl substituents on alkaline hydrolytic reactivity of aliphatic amides.

More recently, the effects of amide structure, hydroxide ion concentration, weak acids and bases, solvent composition, temperature, and other variables on the kinetics of alkaline hydrolysis of amides have been the subjects of a number of investigations. These include studies of hydrolyses of aliphatic amides,[6-9] chloroacetamides,[10] aliphatic and aromatic diamides,[11-15] benzamides,[9,16-18] glycinamide,[19] and urea.[20] Kinetic studies of alkaline hydrolysis of a number of N-substituted amides have also been reported. Most of these investigations concerned acetanilides,[21-23] acyl-substituted acetanilides,[23-32] and *N*-methylanilides.[24,29,33-35] Saponifications of glycylglycine,[36] α-propylamino-2′-methylpropionanilide,[37] and several heterocyclic amides[38-42] have also been studied.

The products of amide hydrolysis in alkaline solutions are carboxylate ions and ammonia or amines (eq 1).

$$RCONR'R'' + OH^- \longrightarrow RCO_2^- + R'R''NH \quad (1)$$

Saponification of simple aliphatic amides,[4-7] benzamides,[2,3,16,17] and a number of diamides[11-15] are first order in hydroxide ion, as would be expected if these reactions occur by the $B_{Ac}2$ mechanism of Ingold.[43]

Amide saponification is sensitive to both polar and steric effects of acyl substituents. Reactivity of aliphatic amides is decreased by alkyl substitution in the acyl substituent R (eq 1), with β-alkyl substituents retarding saponification more than α-alkyl substituents.[4-7,9] Electron-attracting acyl substituents accelerate alkaline hydrolysis of amides, with the result that mono-, di- and trichloroacetamides,[5,10] nitro- and halobenzamides,[2,3,17-19] and halo- and ammonio-substituted acetanilides[24-32] are more reactive than their unsubstituted analogs. In general, acyl substituent effects on alkaline hydrolysis are reflected more in the energy than in the entropy of activation.[6,7,9,17]

It has recently become apparent that carboxamide hydrolysis is mechanistically more complex than previously supposed. Bender and coworkers demonstrated that alkaline hydrolysis of carbonyl-^{18}O-labeled benzamide[16] and several carbonyl-^{18}O-labeled acetanilides[21] is accompanied by partial exchange of solvent oxygen for carbonyl oxygen. This observation indicates that the complexes formed by reaction of hydroxide ion with these amides are neither transition states (in which case no exchange would occur) nor intermediates in equilibrium with the starting materials (in which case complete

(1) Submitted by R. C. N. in partial fulfillment of the requirements for the M.A. (1965) and Ph.D. (1971) degrees at the University of California at Santa Barbara.

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(35) R. L. Schowen and G. W. Zuorick, *ibid.*, **88**, 1223 (1966).
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(37) S. O. Eriksson and J.-O. Omdol, *ibid.*, **1**, 77 (1964).
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(42) I. Blagoeva, B. J. Kurtev, and I. G. Pojarlieff, *J. Chem. Soc. B*, 232 (1970).
(43) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," 2nd ed, Cornell University Press, Ithaca, N. Y., 1969, p 1167.

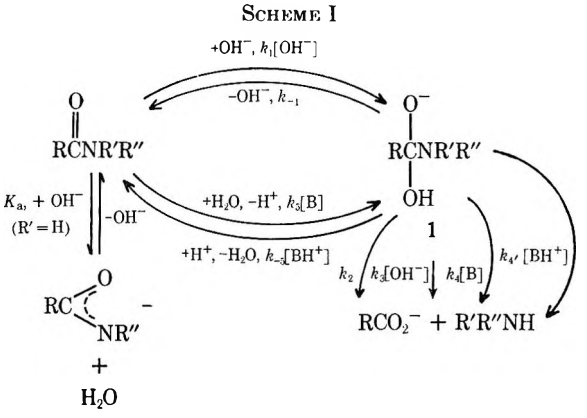
exchange should occur). In addition, rates of hydrolysis of a number of amides exhibit a greater than first-order dependence on hydroxide ion concentration in certain pH ranges. This is true of chloroacetamide,[10] glycinamide,[20] glycylglycine,[36] a number of anilides[22-29,31,32] and *N*-methylanilides,[21,24,33-35] urea,[20] 5,5-dialkylbarbituric acids,[38-40] dihydropyrimidine,[41] and dihydrouracil.[42] The kinetics of many amide hydrolyses are complicated by the fact that the amides exist in equilibrium with unreactive conjugate bases (eq 2). Amides which are sufficiently acidic to form

$$\mathrm{RCONHR'} + \mathrm{OH^-} \rightleftharpoons \mathrm{RC(=O)NR'^-} + \mathrm{H_2O} \qquad (2)$$

appreciable amounts of unreactive conjugate bases at high pH include dichloro- and trichloroacetamide,[10] trichloro- and trifluoroacetanilide,[24-27,31] fluoroacetanilide,[28] trimethylammonioacetanilide,[29] *p*-nitroacetanilide,[23] 5,5-dialkylbarbituric acids,[38-40] dihydropyrimidines,[41] and dihydrouracil.[42] Further, the alkaline hydrolyses of a number of amides (acetanilide,[22] acyl-substituted acetanilides,[25-29,31,32,34,35] and chloramphenicol[30]) are subject to catalysis by general acids and bases.

The work of Eriksson,[22,25-29,38-40] Schowen,[33-35] Mader,[31] Pratt,[32] and Bender[16,21] suggests a mechanism of amide hydrolysis which rationalizes all of the experimental results described above (Scheme I).

SCHEME I



According to this mechanism, amide hydrolysis involves reversible, general base catalyzed formation of an anionic tetrahedral intermediate, followed by general acid–general base catalyzed elimination of ammonia or amine from the intermediate. At sufficiently high pH, some amides dissociate to unreactive conjugate bases in a parasitic side equilibrium.

Assuming validity of the steady-state approximation for the concentration of the tetrahedral intermediate, this mechanism leads to the expression for the observed first-order rate constant, k_{obsd}, for amide hydrolysis in buffer solutions (eq 3).[32] In eq 3, B represents any Brønsted base and BH^+ its conjugate acid.

$$k_{obsd} = \frac{1}{1 + K_a[OH^-]/K_w} \times \left\{ \frac{(k_1[OH^-] + k_5[B])(k_2 + k_3[OH^-] + k_4[B] + k_{4'}[BH^+])}{k_{-1} + k_2 + k_3[OH^-] + k_4[B] + (k_4 + k_{-5})[BH^+]} \right\} \qquad (3)$$

Since experimental evidence supporting the mechanism of Scheme I is convincing in the case of certain acyl-activated anilides, it is reasonable to suppose that this mechanism is also applicable to other anilide hydrolyses. The relative importance of the various terms of eq 3 depends on the structure of the amide and the composition of the reaction medium. In unbuffered solutions eq 3 simplifies to eq 4. If the amide is so weakly

$$k_{obsd} = \frac{k_1[OH^-]}{1 + K_a[OH^-]/K_w} \frac{k_2 + k_3[OH^-]}{k_{-1} + k_2 + k_3[OH^-]} \qquad (4)$$

acidic that it is not appreciably dissociated in such solutions, $K_a[OH^-]/K_w \ll 1$, and eq 4 is further simplified to eq 5. The evidence supporting the mechanism of

$$k_{obsd} = k_1[OH^-] \frac{k_2 + k_3[OH^-]}{k_{-1} + k_2 + k_3[OH^-]} \qquad (5)$$

Scheme I (or one very similar to it) is discussed by Eriksson[39] and Pratt.[32]

While acyl substituent effects on alkaline hydrolytic reactivity of carboxamides have been studied extensively, little is known concerning the effects of amide *N* substituents on reactivity. Our interest in aryl substituent effects on anilide hydrolysis stems from the observation, made in the course of a kinetic study of alkaline *N,N'*-diarylformamidine hydrolysis,[44] that *p*-nitroformanilide hydrolyzes much faster than *m*-chloroformanilide in alkaline aqueous dioxane solutions. Bender and Thomas had previously reported that rates of alkaline hydrolysis of substituted acetanilides $CH_3CONHC_6H_4X$ (X = *p*-CH_3O, *p*-CH_3, H, *p*-Cl, and *m*-NO_2) are almost independent of the nature of the aryl group.[21] Our observation suggested either that aryl substituent effects are quite different for formanilide and acetanilide saponifications or that *p*-nitroformanilide is anomalously reactive.

In order to resolve this discrepancy and obtain additional information relevant to the mechanism of anilide saponification, we studied the effects of substituents on the phenyl group, hydroxide ion concentration, and temperature on the kinetics of alkaline hydrolysis of formanilide, *N*-methylformanilide, and a number of substituted formanilides and *N*-methylformanilides. We also studied the alkaline hydrolysis and concurrent carbonyl–oxygen exchange of *p*-nitroacetanilide. These studies confirmed that *p*-nitroanilides are anomalously reactive.

Experimental Section

Materials.—*p*-Aminobenzonitrile [mp 77–81° (lit.[45] mp 86°)] was prepared by reducing *p*-nitrobenzonitrile according to the procedure of Bogert and Hand.[46] The *p*-nitrobenzonitrile [mp 143–146° (lit.[47] mp 147°)] was obtained by a Sandmeyer reaction of *p*-nitroaniline, carried out according to the procedure of Clarke and Read.[48]

p-Hydroxyformanilide was reduced to *N*-methyl-*p*-aminophenol by the procedure of Ehrlich[49] [mp 85° (lit.[50] mp 85°)]. Other arylamines and *N*-methylarylamines were obtained from Matheson Coleman and Bell, Eastman Organic Chemicals, and Aldrich Chemical Co.

Formanilide and *N*-methylformanilide were used as received from Matheson Coleman and Bell. Other formanilides and *N*-methylformanilides were prepared from arylamines or *N*-methylarylamines and acetic formic anhydride, by the procedure

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of Huffman,[51] with the exception of *N*-methyl-*p*-nitroformanilide and *N*-methyl-*p*-chloroformanilide, which were prepared by reaction of the primary arylamines with triethyl orthoformate in the presence of concentrated sulfuric acid at elevated temperatures.[52] Properties of the formanilides and *N*-methylformanilides are listed in Table I.

TABLE I

PROPERTIES OF FORMANILIDES, XC_6H_4NRCHO

	R = H		R = CH_3	
X	Mp or bp (mm), °C	Lit. mp	Mp, °C	Lit. mp
p-NO_2	192–194	194–195[a]	116	118–120[m]
m-NO_2	134	134[b]	68–69	70–71[b]
m-Cl	56–57	57–58[c]		
p-Cl	92	102[d]	48–50	51[n]
p-Br	117	119[e]		
p-CH_3	47–51	52[f]		
m-CH_3	137 (1)	18[g]		
p-CH_3O	78–80	80–81[h]		
m-CH_3O	55–57	57[i]		
p-$(CH_3)_2N$	108	108[j]		
p-CN	189	188–189[k]		
p-OH	138–139	139–140[l]	106	108–109[o]

[a] G. T. Morgan and F. G. M. Michelwait, *J. Chem. Soc.*, **87**, 931 (1905). [b] W. J. Comstock and H. L. Wheeler, *Amer. Chem. J.*, **13**, 516 (1891). [c] O. C. M. Davis, *J. Chem. Soc.*, **95**, 1398 (1909). [d] F. D. Chattway, K. J. P. Orton, and W. H. Hurtley, *Chem. Ber.*, **32**, 3636 (1899). [e] M. Dennstedt and P. Groth, *Chem. Kryst.*, **4**, 224 (1910). [f] M. D. Farrow and C. K. Ingold, *J. Chem. Soc.*, **125**, 2546 (1924). [g] St. Niementowski, *Chem. Ber.*, **20**, 1892 (1877). [h] E. Froelich and E. Wedekind, *ibid.*, **40**, 1009 (1907). [i] F. Reverdin and A. LeLuc, *ibid.*, **47**, 1539 (1914). [j] J. Pinnow and G. Pistor, *ibid.*, **26**, 1313 (1893). [k] M. Bogert and L. Wise, *J. Amer. Chem. Soc.*, **33**, 1494 (1910). [l] H. E. Fierz-David and W. Kuster, *Helv. Chim. Acta*, **22**, 82 (1939). [m] G. T. Morgan and W. R. Grist, *J. Chem. Soc.*, **113**, 690 (1918). [n] See ref 52. [o] M. Sekiya, M. Tomie, and N. Leonard, *J. Org. Chem.*, **33**, 321 (1968).

p-Nitroacetanilide-*carbonyl*-^{18}O (mp 212.5–213°) was prepared by acetylation of *p*-nitroaniline with carbonyl-^{18}O enriched acetyl chloride. The labeled acetyl chloride was obtained by hydrolyzing acetyl chloride in water enriched with ^{18}O (1.6 atom % ^{18}O, Bio-Rad Laboratories), allowing the hydrolysis mixture to equilibrate for 1 week, and converting the recovered ^{18}O-labeled acetic acid to acetyl chloride with PCl_3.

Rate Measurements.—The hydrolysis reactions, which are first order under the conditions used, were followed spectrophotometrically with a Gilford Model 2000 recording spectrophotometer equipped with a thermostated cell compartment. Temperature control was to within 0.01°. Reactions were followed by recording the change in absorbance at the wavelength of maximum difference in absorbance between the anilide and the arylamine product. Spectra of reaction solutions made after complete hydrolysis showed that the arylamines were the only aromatic products. Reaction solutions were prepared by adding enough of a 0.01 *M* solution of the anilide in absolute ethanol to a carbonate-free aqueous sodium hydroxide solution to give a solution which contained 1.00% ethanol and was 10^{-4} *M* in anilide. Except where noted, the ionic strength of the reaction solutions was adjusted to 1.00 by use of sodium chloride. First-order rate constants were calculated graphically from plots of ln $(A_\infty - A_t)$ *vs.* time (in seconds) or by means of a computer program which calculated the first-order rate constant which best fits the experimental data. Reactions were followed for at least 3 half-lives and usually for 10 half-lives. All rate constants listed in the tables are averages of two or more runs, with agreement between runs usually being within 3%. Energies of activation were calculated from the Arrhenius equation by the least-squares method. Entropies of activation were calculated for 25° as described by Bunnett, using the Arrhenius activation energies and preexponential factors.[53]

Determination of pK_a Values of Anilides.—The pK_a's of *p*-nitroformanilide and *p*-nitroacetanilide were determined spectrophotometrically. Since these compounds hydrolyze rapidly in alkaline solutions, it was necessary to extrapolate to zero time to determine the absorbance of the anilide at each hydroxide ion concentration. Ionic strength was 1.0 for all solutions except those for which $[OH^-]$ was more than 1.0. Since neither of the anilides is completely dissociated at the highest hydroxide ion concentrations used, pK_a values were calculated using the method of Hine and Hine.[54] The pK_a of *p*-nitroformanilide, calculated from absorbance values from $[OH^-]$ = 0.010–1.000 *M*, is 12.5 at 30° and 12.8 at 15°. The pK_a of *p*-nitroacetanilide, calculated from absorbance values from $[OH^-]$ = 0.010–4.00 *M*, is 13.6 at 30°.

pH–absorbance profiles for *p*-hydroxyformanilide and *N*-methyl-*p*-hydroxyformanilide show that the pK_a values for dissociation of the phenolic proton of these compounds at 30° are 9.2 and 9.0, respectively. These compounds were therefore present as phenoxide ions under the conditions of the kinetic experiments.

Oxygen Exchange of *p*-Nitroacetanilide.—Samples of *p*-nitroacetanilide-*carbonyl*-^{18}O were partially hydrolyzed under the conditions used in the kinetic runs. Sample size was such as to permit recovery of 0.1 mmol of unhydrolyzed anilide. Samples were quenched by addition of sufficient HCl to neutralize the NaOH and immediately extracted 6–8 times with ethyl ether. Evaporation of the ether yielded mixtures and *p*-nitroacetanilide and *p*-nitroaniline, which were separated by thick layer chromatography on silica gel GF 254 (Brinkman Instruments, Inc.). The recovered anilide was recrystallized from benzene and degraded by the procedure of Rittenberg and Pontecorvo,[55] and the resulting CO_2 was analyzed by means of a Consolidated Electrodynamics Model 21-620 mass spectrograph to determine the ratios of the mass 44 and mass 46 peaks. The atom fraction of ^{18}O in the CO_2 was calculated according to Roberts and Urey,[56] and rates of ^{18}O exchange were calculated as described by Bender.[57]

Results

Rate constants for alkaline hydrolysis of a number of formanilides and *p*-nitroacetanilide are collected in Table II, and rate constants for alkaline hydrolysis of several *N*-methylformanilides appear in Table III.

With the exception of *p*-nitroformanilide and *p*-cyanoformanilide, the rate of alkaline hydrolysis of formanilides is independent of substituents on the aryl group, regardless of the temperature and hydroxide ion concentration (Figures 1 and 2). (In Figures 1–3, σ^- values[58] are used for *p*-CN and *p*-NO_2.) Calculated ρ values and standard errors of fit of the log k values to the least-squares regression lines follow: at 15°, 0.200 *N* NaOH, $\rho = +0.046$, $S_y = 0.054$; at 29.9°, 0.200 *N* NaOH, $\rho = -0.057$, $S_y = 0.083$; at 44.2°, 0.50 *N* NaOH, $\rho = +0.019$, $S_y = 0.062$; at 44.2°, 0.100 *N* NaOH, $\rho = -0.015$, $S_y = 0.062$; at 44.2°, 0.500 *N* NaOH, $\rho = -0.080$, $S_y = 0.078$. Under a given set of experimental conditions, *p*-cyanoformanilide is several times more reactive, and *p*-nitroformanilide is several hundred times more reactive, than the other formanilides.

In contrast to the formanilides, *N*-methylformanilide hydrolysis is accelerated by electron-withdrawing aryl substituents in 1.00 *N* NaOH solutions at 29.9° (Figure 3). The Hammett plot of these data is concave upward.

As shown in the pH–hydrolysis rate profiles of Figures 4–6, anilide hydrolysis rates are complex functions

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(52) R. M. Roberts and P. J. Vogt, *J. Amer. Chem. Soc.*, **78**, 4778 (1956).
(53) J. F. Bunnett in "Technique of Organic Chemistry," Vol. III, Part I, A. Weissberger, Ed., Interscience, New York, N. Y., 1961, p 201.
(54) J. Hine and M. Hine, *J. Amer. Chem. Soc.*, **74**, 5266 (1952).
(55) D. Rittenberg and L. Pontecorvo, *Intern. J. Appl. Radiat. Isotop.*, **1**, 208 (1956).
(56) I. Roberts and H. Urey, *J. Amer. Chem. Soc.*, **61**, 2580 (1939).
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(58) H. H. Jaffé, *Chem. Rev.*, **53**, 222 (1953).

TABLE II

HYDROLYSIS OF ANILIDES IN AQUEOUS 1% ETHANOL–SODIUM HYDROXIDE SOLUTIONS

[OH⁻]	10^4k_{exp}, sec⁻¹, at T, °C 1.2°	15.0°	29.9°	44.2°
	p-Nitroformanilide			
0.010	2.4[a]		21.2[b]	33[b]
0.020	6.6	21.4	51	94
0.050	17.7		160	330
0.067			200	450
0.100	29.5	110	300	620
0.200	46	130	430	930
0.333		180	470	
0.500	50	170	510	1300
0.667		170	510	1400
1.00		220	510	1300
	p-Cyanoformanilide			
0.010			0.12[b]	0.30[b]
0.020			0.34	0.93
0.033				2.0
0.050			1.42	4.2
0.067			2.23	6.2
0.100			4.1	11.0
0.200			(9.1)[c]	25
0.333			16.4	36
0.500			24	67
0.667			33	91
1.00			52	138
	m-Nitroformanilide			
0.0050			0.021[a]	
0.010			0.059	
0.050			0.49	
0.100			1.0	2.04[a]
0.200			(1.8)[d]	
	m-Chloroformanilide			
0.050		0.087		0.59[a]
0.100		0.22		1.24
0.200		0.63	1.30[a]	3.0
0.500		1.7	3.30	8.6
	p-Bromoformanilide			
0.050		0.087[a]		0.57[a]
0.100		0.23		1.25
0.200		0.61	1.38[a]	2.6
0.500		2.2		9.6
	p-Chloroformanilide			
0.067				0.88[b]
0.100				1.51
0.200		0.75[b]	1.7[b]	3.5
0.333		1.59	2.9	6.7
0.500		3.0	5.6	10.2
0.600			6.8	
0.667		3.8		15.2
0.800		6.8	9.6	

[OH⁻]	10^4k_{exp}, sec⁻¹, at T, °C 1.2°	15.0°	29.9°	44.2°
	Formanilide			
0.067			0.38[b]	
0.100			0.66	1.45[a]
0.200			1.75	3.3
0.333			3.6	
0.500		2.6[a]	6.4	11.1
0.667			10.1	
1.00			15.6	
	m-Formtoluidide			
0.050				0.54[a]
0.100		0.19[a]		1.18
0.200		0.55	1.24[a]	1.74
0.500		2.1		10.7
	p-Formtoluidide			
0.050				0.47[a]
0.100		0.22[a]		1.01
0.200		0.53	1.21[a]	2.63
0.500		3.2		6.8
	p-Methoxyformanilide			
0.050		0.091[a]		0.56[a]
0.100		0.25	0.59[a]	1.14
0.200		0.72	1.6	2.6
0.500		3.0	5.5	8.5
	p-Dimethylaminoformanilide			
0.010			0.027[b]	0.097[b]
0.020			0.073	0.20
0.050			0.23	0.58
0.067			0.35	
0.100			0.57	1.57
0.200			2.3	3.8
0.333			3.4	7.3
0.500			6.5	13.1
0.667			10.2	20.2
1.00			16.9	34
	p-Formylphenoxide Ion			
1.00			16.5[b]	
	p-Nitroacetanilide			
0.010			0.051[b]	0.148[b]
0.020			0.150	0.44
0.033			0.34	0.97
0.050			0.65	1.82
0.067			0.98	2.8
0.100			1.74	5.0
0.200			3.8	11.3
0.333			5.6	16
0.500			8.2	26
0.677			9.7	31
1.00			11.8	37

[a] Ionic strength = 0.500. [b] Ionic strength = 1.00. [c] Interpolated value. [d] Extrapolated value.

of hydroxide ion concentration. The pH–log rate plots are curved for most of the anilides studied. Apparent kinetic orders with respect to hydroxide ion in 0.01 *N* NaOH solutions range from 1.4 to 1.6 for all of the formanilides except *p*-dimethylaminoformanilide at 44.2°, whose hydrolysis is about 1.1 order in hydroxide ion at pH 12, increasing to 1.4 order at pH 14. The pH–log rate curves for *m*- and *p*-nitroformanilides, *p*-cyanoformailide, and *p*-nitroacetanilide all exhibit downward curvature due to partial dissociation of the anilides to unreactive conjugate bases in the more concentrated sodium hydroxide solutions.

The apparent kinetic order in hydroxide ion for hydrolysis of *N*-methylformanilide and its *m*-nitro and *p*-chloro derivatives is 2.0 at pH 14 and decreases with decreasing pH. The apparent kinetic order with respect to hydroxide ion for hydrolysis of *N*-methyl-*p*-nitroformanilide is about 1.5 at pH 14 and 1.0 at pH 12.5.

Arrhenius activation energies and entropies of activation for hydrolysis of several formanilides in 0.200 *N* NaOH are recorded in Table IV. For all of the formanilides except the *p*-cyano and *p*-nitro derivatives, the energies of activation cluster around 9 kcal/mol and the entropies of activation cluster around −46 eu. The differences between E_a and $\Delta S^{\pm}$ values for hydrolysis of these anilides are no greater than the probable errors of the calculated values. For *p*-cyano- and *p*-nitroformanilides, the energies of activation are somewhat

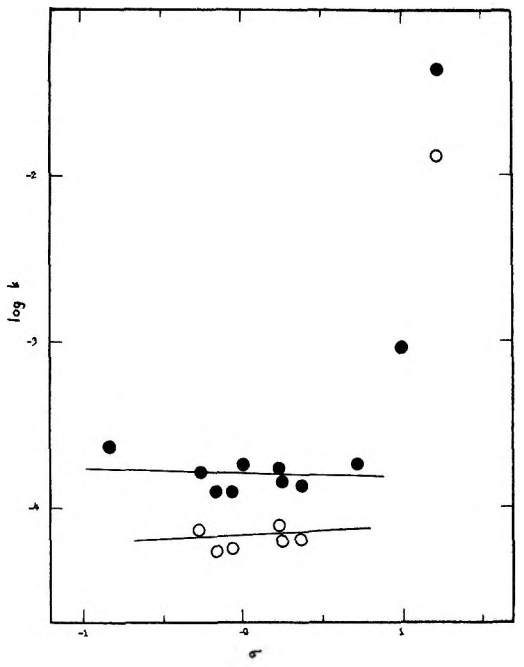


Figure 1.—Hammett plots for hydrolysis of formanilides in 0.200 *N* NaOH at 15.0 and 29.9°: ●, 29.9°; ○, 15.0°.

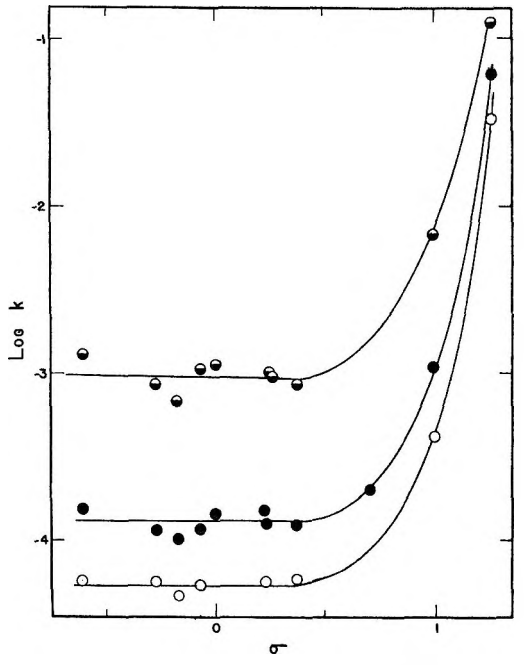


Figure 2.—Hammett plots for hydrolysis of formanilides at 44.2°: ○, in 0.050 *N* NaOH; ●, in 0.100 *N* NaOH; ◒, in 0.500 *N* NaOH.

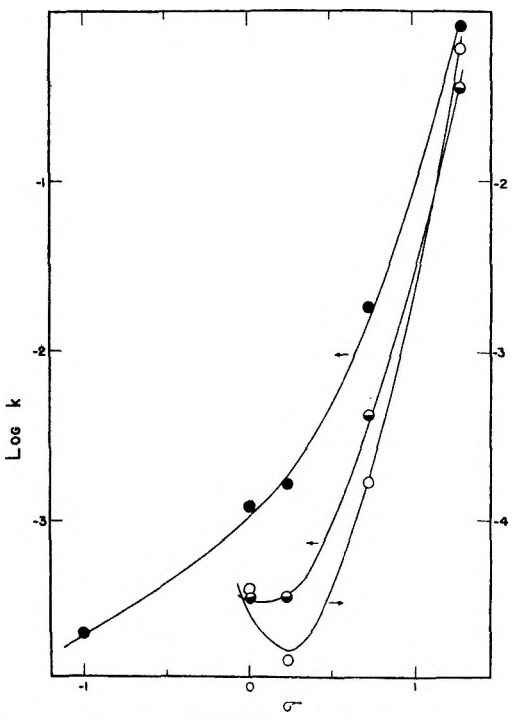


Figure 3.—Hammett plots for hydrolysis of *N*-methylformanilides at 29.9°: ●, in 1.00 *N* NaOH; ◒, in 0.500 *N* NaOH; ○, in 0.100 *N* NaOH.

Table III

Hydrolysis of *N*-Methylformanilides, $XC_6H_4N(CH_3)CHO$, in Aqueous 1% Ethanol–Sodium Hydroxide Solutions at 29.9°

	10^4k_{exp}, sec^{-1} [a]				
[OH$^-$]	X = *p*-NO_2[b]	X = *m*-NO_2[c]	X = *p*-Cl[d]	X = H[e]	X = *p*-O$^-$[f]
0.010		0.077	0.0058		
0.020	105		0.0116		
0.050	295	0.68	0.043		
0.100	610	1.70	0.151	0.40	
0.200	1200		0.58	0.95	
0.250		8.7			
0.300			1.27		
0.333				1.82	
0.500	3600	42	3.60	3.7	
0.600			5.4		
0.667				6.2	
0.700			7.5		
0.800			9.8		
0.900			12.6		
1.00	8200	187	16.4	12.7	2.18

[a] Ionic strength = 1.00. [b–f] Registry no. are as follows: [b] 5279-61-8; [c] 31947-47-4; [d] 26772-93-0; [e] 93-61-8; [f] 31947-49-6.

larger, and the entropies of activation are more than 12 eu less negative, than for the other formanilides.

Hydrolysis experiments with carbonyl-^{18}O-labeled *p*-nitroacetanilide demonstrated that this acetanilide, like acetanilide and its *m*-nitro, *p*-chloro, *p*-methyl, and *p*-methoxy derivatives (previously studied by Bender and Thomas[21]), undergoes concurrent hydrolysis and carbonyl oxygen exchange in alkaline solutions. The results of these experiments, summarized in Table V, show that the rate of hydrolysis is more sensitive to hydroxide ion concentration than is the rate of oxygen exchange. In this respect *p*-nitroacetanilide resembles the acetanilides studied previously.[21]

Table IV

Energies and Entropies of Activation for Hydrolysis of Formanilides, XC_6H_4NHCHO, in 0.2 *N* NaOH

X	Registry no.	$10^{-3}E_a$, cal/mol	$\Delta S^{\pm}$[a], eu
p-NO_2	16135-31-2	12.4	−31
p-CN	6321-94-4	13.5	−33
m-Cl	139-71-9	9.7	−46
p-Br	2617-78-9	9.0	−48
p-Cl	2617-79-0	9.6	−46
m-CH_3	3085-53-8	10.1	−45
p-CH_3	3085-54-9	10.0	−46
p-CH_3O	5470-34-8	8.0	−49

[a] Calculated for 25°.

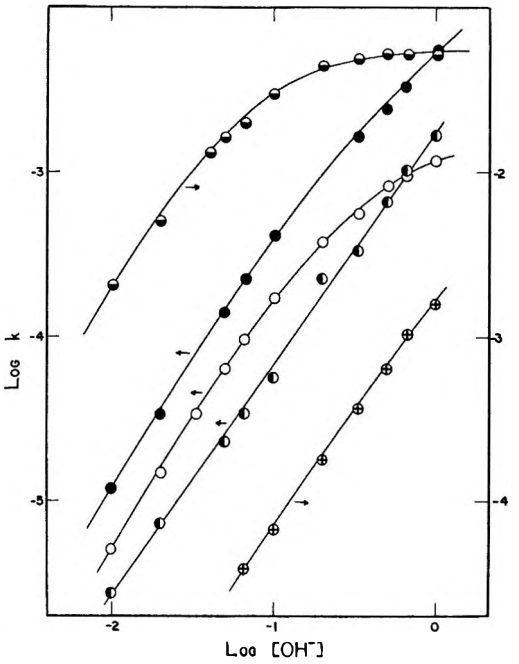


Figure 4.—Representative rate-pH profiles for hydrolysis of anilides at 29.9°: ◒, *p*-nitroformanilide; ●, *p*-cyanoformanilide; ○, *p*-nitroacetanilide; ◐, *p*-dimethylaminoformanilide; ⊕, formanilide.

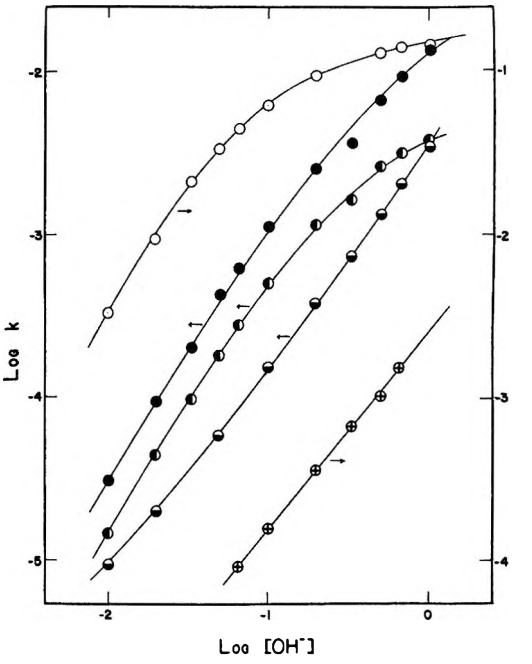


Figure 5.—Representative rate-pH profiles for hydrolysis of anilides at 44.2°: ○, *p*-nitroformanilide; ●, *p*-cyanoformanilide; ◐, *p*,nitroacetanilide; ◒, *p*-dimethylaminoformanilide; ⊕, *p*-chloroformanilide.

TABLE V

OXYGEN EXCHANGE DATA FOR *p*-NITROACETANILIDE-^{18}O IN AQUEOUS 1% ETHANOL AT 30°, μ = 1.00

[OH⁻]	$10^6 k_h$, sec^{-1}	$10^6 k_{ex}$, sec^{-1}	k_h/k_{ex}
0.02	1.50	2.56	0.625
0.05	6.52	5.41	1.20
0.10	17.4	7.64	2.28
0.24			~6[a]

[a] Extrapolated value.

We observed small positive salt effects on alkaline formanilide hydrolysis. Typically, hydrolysis rate increases 10–15% when the ionic strength is increased from 0.5 to 1.0.

Discussion

If the *p*-cyano and *p*-nitro derivatives are omitted, Hammett ρ values for formanilide saponification are approximately 0 in the temperature range 15–45° and in the hydroxide concentration range 0.05–0.50 *N*. Bender and Thomas observed similarly small substituent effects on acetanilide hydrolysis[21] and showed that the approximately 0 ρ value for acetanilide saponification is due to the fact that the positive ρ value for formation of tetrahedral intermediate **1** (Scheme I) from hydroxide ion and the anilide is numerically equal to the negative ρ value for partitioning of **1** between products and starting materials. It is quite probable that a similar explanation accounts for the 0 ρ value for formanilide hydrolysis.

The complete Hammett plots for formanilide hydrolysis (Figure 1 and 2) curve upward sharply for substituents having large positive σ values. *p*-Cyanoformanilide is about ten times as reactive, and *p*-nitroformanilide is about 100 times as reactive, as other formanilides. In order to eliminate the possibility that the anamolous reactivity of *p*-nitroformanilide might be due to incursion of a mechanism of hydrolysis involving preliminary formyl proton abstraction, we studied the kinetics of

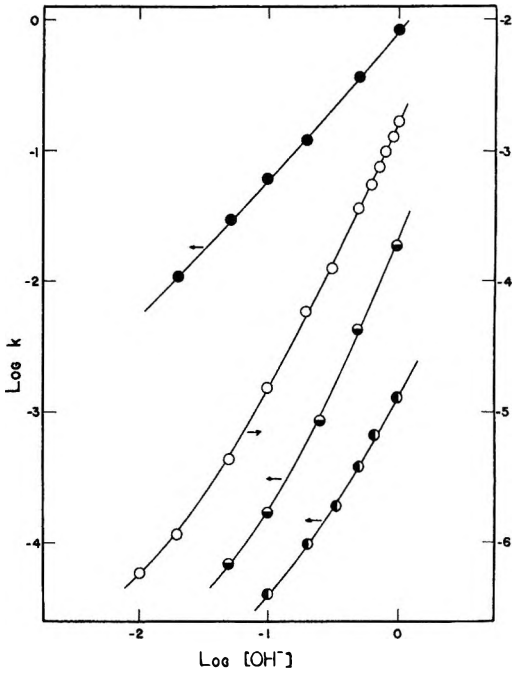


Figure 6.—Rate-pH profiles for hydrolysis of *N*-methylformanilides at 29.9°: ●, *N*-methyl-*p*-nitroformanilide; ○, *N*-methyl-*p*-chloroformanilide; ◒, *N*-methyl-*m*-nitroformanilide; ◐, *N*-methylformanilide.

alkaline hydrolysis of *p*-nitroacetanilide (see Table II). This anilide also is more than 100 times as reactive as other acetanilides.

According to the mechanism of Scheme I, hydrolysis products in unbuffered alkaline solutions are formed from anionic tetrahedral intermediate **1** by competing reactions which are zero order and first order in hydroxide ion. The influence of aryl and acyl substituents on values of k_1 and the partitioning ratios k_2/k_{-1} and k_3/k_{-1} illuminates the mechanism of anilide hydrolysis. These values, which can be calculated from rates of

isotope exchange, rates of hydrolysis, and pK_a values of various aryl- and acyl-substituted acetanilides, are summarized in Table VI.

Table VI

Values of k_1 and Partitioning Ratios for Alkaline Hydrolysis of $YCONHC_6H_4X$

Y	X	10^5k_1, M^{-1} sec^{-1}	k_2/k_{-1}	k_3/k_{-1}, M^{-1}	k_3/k_2, M^{-1}
CH_3	p-CH_3O[a]	4.20[h]	0.195	0.160	0.82
CH_3	p-CH_3[a]	4.85[h]	0.146	0.084	0.57
CH_3	H[a]	7.85[h]	0.097	0.047	0.49
		7.85[i,j]	0.084	0.053	0.63
CH_3	p-Cl[a]	12.7[h]	0.055	0.051	0.91
CH_3	p-NO_2[b]	368[h]	0.077	10.6	138
		470[i]	0.05	8.0	160
CH_2F	H[c,d]	1370[i]	0.021	0.75	36
$(CH_3)_3NCH_2$	H[c,e]	1230[i]	0.0030	0.37	123
CCl_3	H[c,f]	15,500[i]	0.025	34	136
CF_3	H[c,f]	155,500[i]	0.025	93	372
$CHCl_2$	p-NO_2[g]	3,900,000[i]	0.05	6130	

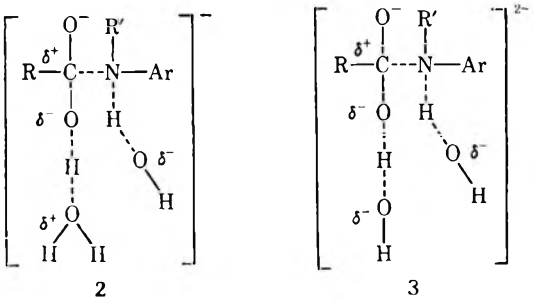
[a] Reference 21, T = 24.7°. [b] Present work, T = 30.0°. [c] Rates measured in aqueous 9.6% ethanol at 25.0°. [d] Reference 28. [e] Reference 29. [f] Reference 27. [g] Reference 32, T = 40°. [h] Data in this row calculated from kinetics of hydrolysis and isotope exchange. [i] Data in this row calculated from kinetics of hydrolysis. [j] Reference 22, T = 25°.

The data of Table VI show that electron-attracting substituents on the aryl group increase the rate of formation of the tetrahedral intermediate **1** (k_1 of Scheme I) but are less effective in doing so than electron-attracting acyl substituents. The partitioning ratio k_2/k_{-1} is insensitive to inductive effects of acyl substituents (as expected, since acyl substituents should affect departure of anilide or hydroxide about equally) but is influenced by aryl substituents. Electron-withdrawing substituents on the aryl group decrease k_2/k_{-1}, presumably by diminishing the basicity of anilino nitrogen and so reducing the effectiveness of water as a general acid catalyst in the product-forming step. Values of k_2/k_{-1} show that intermediate **1** reverts to anilide and hydroxide ion 5–40 times faster than it undergoes conversion to products. In contrast, the ratio k_3/k_{-1} is strongly affected by electron-attracting substituents in either the acyl or aryl group of the anilide. For p-nitroacetanilide,trichloro- and trifluoroacetanilides, and p-nitrodichloroacetanilide, k_3/k_{-1} and k_3/k_2 are both much larger than unity. For these anilides, hydroxide ion catalyzed conversion of **1** to products is much faster than reversion of **1** to starting materials at high pH, and formation of **1** becomes rate limiting.

A Hammett plot of log k_1 *vs.* σ is linear with positive slope for all of the acetanilides, including the p-nitro derivative. The Hammett plot of log k_2/k_{-1} *vs.* σ is linear with negative slope for all of the acetanilides except p-nitroacetanilide, whose point is above the line defined by the other points. In contrast, a Hammett plot of log k_3/k_{-1} *vs.* σ is strongly concave upward, passing through a minimum at approximately $\sigma = 0$. This suggests that the mechanism of the third-order hydrolytic pathway changes as the electronic properties of the aryl group changes and that the anomalous reactivity of p-nitroacetanilide is a consequence of its reacting mainly *via* a different mechanism from the other anilides, at least in the pH range 12–14.

p-Cyano- and p-nitroformanilides also appear to hydrolyze by a different mechanism than the other formanilides at high pH. The nonlinear Hammett plots of log k_{obsd} *vs.* σ (Figures 1 and 2) suggest a shift in mechanism, and the fact that the entropies of activation for hydrolysis of the p-nitro- and p-cyanoformanilides are some 15 eu less negative than the entropies of activation for the other formanilides also suggests that formanilides hydrolyze by two different mechanisms. Further, for p-nitroformanilide hydrolysis it is possible to calculate k_1 and k_3/k_{-1} from kinetic data and the pK_a of the anilide. The values of these parameters which best reproduce the experimental data when inserted into eq 4 are $k_1 = 1.9\ M^{-1}$ sec^{-1} and $k_3/k_{-1} = 16\ M^{-1}$ (standard error in log k = 0.021 using these values; the fit is not improved by inclusion of a k_2/k_{-1} term, which means that k_3/k_2 is much larger than unity). The value of k_3/k_{-1} is similar to the values calculated for p-nitroacetanilide hydrolysis and is much larger than values calculated for the other acetanilides.

The product-forming step in the hydrolysis of anilides lacking strongly electron-attracting substituents on the aryl group probably involves simultaneous proton removal from the hydroxyl group of intermediate **1** by hydroxide ion or a general base and proton transfer to anilino nitrogen from water or a general acid. This conclusion is supported by the observed general acid–general base catalysis of anilide hydrolysis,[32,35,39] by solvent–deuterium isotope effects,[34] and by the fact that both k_2/k_{-1} and k_3/k_{-1} decrease when the water content of the solvent decreases.[22] The large negative entropies of activation for formanilide hydrolysis in alkaline solutions (Table IV) suggest that transition states for anilide hydrolysis involve considerable bound water. **2** and **3** are possible structures for transition states for second- and third-order hydrolysis of "typical" anilides. Water undergoing covalency change, but not hydrogen-bonded water of solvation, is shown in these structures.



2 **3**

Hydrolysis reactions proceeding *via* transition states **2** and **3** involve general acid catalyzed fission of the acyl carbon–anilino nitrogen bond. General base catalyzed dissociation of the tetrahedral intermediate to a carboxylate ion and an arylamide ion would involve cleavage of a strong carbon–nitrogen bond and formation of a strongly basic amide ion. This apparently is energetically unfeasible for most carboxanilides and, in accordance with the dictum that general acid catalysis becomes important when it is most needed, cleavage of the C–N bond is general acid catalyzed.

Hydrolyses of p-nitroanilides (and probabyl p-cyanoformanilide and p-formylacetanilide) probably differ from other anilide hydrolyses in not requiring general acid catalysis for fission of the C–N bond. The acyl

carbon–anilino nitrogen bonds in these compounds are weakened by the inductive effect of the aryl substituent, and the arylamide ions formed by C–N bond cleavage are stabilized by resonance interactions between amide nitrogen and the *p*-nitro or *p*-cyano groups.

The large values of k_3/k_2 for *p*-nitroanilide hydrolyses mean that most of the hydrolysis of these compounds at high pH proceeds *via* a process which is second order in hydroxide ion. Thus, the transition state for product formation has two negative charges. Two possible mechanisms which would yield arylamide ions as intermediates from doubly charged transition states are hydroxide ion catalyzed elimination of arylamide ion from **1** and dissociation of a dinegative ion **4**, in equilibrium with **1** (eq 6).

$$1 + OH^- \underset{+H_2O}{\overset{-H_2O}{\rightleftharpoons}} \underset{\underset{O^-}{|}}{\overset{O^-}{|}}{RCNHAr} \longrightarrow RCO_2^- + ArNH^- \qquad (6)$$

4

4 is more likely to be an intermediate in hydrolyses of anilides having strongly electron-attracting substituents (such as *p*-nitro) than in hydrolyses of other anilides because these substituents increase the acidity of the hydroxyl group of **1**. Pollack and Bender recently reported that the solvent–deuterium isotope effect on hydrolysis of *p*-nitroacetanilide in 0.0046 *M* OH^- at 25° is $k_{H_2O}/k_{D_2O} = 0.61$.[23] This isotope effect is consistent with the mechanism of eq 6.

Pollack and Bender assumed that, at 25° in the pH range 12–14, *p*-nitroacetanilide hydrolyzes exclusively according to eq 6. Actually, a fraction of the reaction at the lower end of the pH range probably yields products from a water-catalyzed reaction of intermediate **1**. In fitting Pollack and Bender's data to eq 4, a better fit results if a k_2/k_{-1} term is included than if it is not. The best fit was obtained using $K_a = 1.6 \times 10^{-14}$, $k_3/k_{-1} = 9.0\ M^{-1}$, $k_2/k_{-1} = 0.015$ and $k_1 = 2.25 \times 10^{-3}\ M^{-1}\ sec^{-1}$. The best fit between calculated and observed rate constants for hydrolysis of *p*-nitroacetanilide at 30° (Table II) is obtained by using eq 4 with $K_a = 2.5 \times 10^{-14}$, $k_3/k_{-1} = 8.0\ M^{-1}\ sec^{-1}$, $k_2/k_{-1} = 0.05$, and $k_1 = 4.7 \times 10^{-3}\ sec^{-1}$ (standard error in log *k* using these values is 0.012). We conclude that a small part (about 35% at pH 12; less than 1% at pH 14) of the hydrolysis of *p*-nitroacetanilide proceeds through a singly negatively charged transition state, probably **2**.

The pH profiles for anilide saponification are complex and differ depending on the structure of the aryl group (see Figures 4 and 5). At sufficiently low hydroxide ion concentration (below pH 12 for all of the anilides of this study), all of the products are formed by the k_2 step of Scheme I, and k_{obsd} is first order in hydroxide ion. As the hydroxide ion concentration increases, a point is reached at which a significant amount of product is formed by the k_3 step, and the kinetic order in hydroxide gradually increases toward 2. If the anilide has electron-withdrawing acyl or aryl substituents, the observed kinetic order in hydroxide ion is unlikely to reach a limiting value of 2 for two reaons: first, the anilide is sufficiently acidic to partly dissociate to an unreactive conjugate base at high pH (eq 2); and, second, k_3/k_{-1} is much larger than unity for these activated anilides, so that formation of tetrahedral intermediate **1** rather than its conversion to products becomes rate limiting at high pH. These two factors combine to cause k_{obsd} to level off to a constant value at sufficiently high pH.

If k_{obsd} is corrected for the protolytic equilibrium of eq 2, it is anticipated that the slope of the rate–pH profile for an activated anilide would increase from 1 to 2 and then diminish to 1 again as the pH is increased over a wide range. Such plots of k_{corr} *vs.* pH [$k_{corr} = k_{obsd}(1 + K_a[OH^-]/K_w)$] for *p*-nitroformanilide and *p*-nitroacetanilide show the expected trends. In the pH range 12–14, the slope of the k_{corr} *vs.* pH plot for hydrolysis of *p*-nitroformanilide at 30° diminishes from 1.65 to 1.0. A similar plot for hydrolysis of *p*-nitroacetanilide at 30° diminishes in slope from 1.7 to 1.1.

Hydrolysis of *N*-methylanilides is not complicated by the parasitic equilibrium of eq 2. Otherwise, the *N*-methylanilides probably hydrolyze by essentially the same mechanisms as ordinary anilides. The hydrolysis reactions are general acid–general base catalyzed,[29,33–35] show mixed and variable kinetic orders with respect to hydroxide ion, and in the case of *N*-methylformanilides yield Hammett plots which are concave upward (Figure 3).

N-Methylformanilides (see Figure 6), *N*-methyltrimethylammonioacetanilide,[29] and a number of other acyl-substituted *N*-methylacetanilides[24] exhibit pH–hydrolysis rate profiles whose slopes increase with increasing pH. The observed pH profiles indicate that product formation *via* the k_3 step of Scheme I becomes important at high pH and further (since slopes of the pH profiles do not decrease at the highest pH) that k_3/k_{-1} and k_2/k_{-1} are both smaller than unity; that is, formation of tetrahedral intermediate **1** does not become rate limiting for these anilides, even at high pH.

The limited data available indicate that *N*-methyl substitution in an anilide increases k_2/k_{-1} (Table VII).

TABLE VII

EFFECT OF *N*-METHYL SUBSTITUTION ON k_2/k_{-1} FOR ANILIDE HYDROLYSIS

Anilide	k_2/k_{-1}, R = H	k_2/k_{-1}, R = CH_3
$CF_3CONRC_6H_5$	0.025[a]	0.2[b]
$CH_3CONRC_6H_4$-*p*-NO_2	0.077[c]	1.1[d]

[a] Reference 27, $T = 25°$. [b] Reference 34, $T = 25°$. [c] Present work, $T = 30°$. [d] R. F. Pratt, Ph.D. Dissertation, University of Melbourne, Australia, 1969.

This may be due in part to the greater release of steric crowding when the tetrahedral intermediate from an *N*-methylanilide is converted to products.

In contrast to alkaline hydrolysis of unactivated formanilides and acetanilides, which give Hammett plots of approximately zero slope at several hydroxide ion concentrations, there is an indication that Hammett plots of hydrolysis of unactivated *N*-methylformanilides have slopes which vary with the hydroxide ion concentration. The limited data available (see Figure 3) indicate that plots of log k_{obsd} *vs.* σ have positive slopes at high hydroxide ion concentration and negative slopes at low hydroxide ion concentration. This indicates that ρ for k_3/k_{-1} is less negative than ρ for k_2/k_{-1}, which is opposite to the situation with acetanilides having no *N*-methyl substituent (Table VI).

The anomalous accelerating effect of electron-attracting substituents on hydrolysis rate is even more striking in the case of *N*-methylformanilides than in the case of formanilides: *N*-methyl-*m*-nitroformanilide is about ten times as reactive, and *N*-methyl-*p*-nitroformanilide is about a thousand times as reactive, as *N*-methylformanilide. The explanation of the enhanced reactivity of nitro-substituted *N*-methylformanilides is probably the same as for other anilides: strongly electron-attracting aryl substituents cause a change in mechanism from that of Scheme I to that of eq 6. This view is supported by the fact that the effect of the *p*-nitro group on the entropy of activation for hydrolysis of *N*-methyl-*p*-nitroformanilide is similar to its effect on the entropy of activation for hydrolysis of *p*-nitroformanilide: the entropy of activation for *N*-methyl-*p*-nitroformanilide hydrolysis in 0.2 *N* NaOH (−18 eu) is more than 20 eu less negative than that for hydrolysis of a more typical anilide, *N*-methyl-*p*-chloroformanilide (−41 eu).

Registry No.—*m*-Nitroformanilide, 102-38-5; formanilide, 103-07-8; *p*-dimethylaminoformanilide, 18606-63-8; *p*-formylphenoxide ion, 18938-17-5; *p*-nitroacetanilide, 104-04-1.

Acknowledgment.—The authors acknowledge the capable assistance of M. Andrews, W. Duke, A. Imrie, R. Mann, B. Merrick, E. Serros, J. White, and J. Wolf, who measured some of the reaction rate constants reported in Tables II and III.

Reactions of Nitrosobenzene and Azoxybenzene with Benzene, Benzene-d_6, and Cyclohexane at 600°

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Received September 23, 1970

Nitrosobenzene reacts with benzene at 200–400° to give mostly azoxybenzene and nitrobenzene. At 500–600° the major products are diphenylamine, biphenyl, phenol, and phenylcarbazoles. Minor products include nitrobenzene, triphenylamine, aminobiphenyl, carbazole, hydroxybiphenyl, diphenyl ether, and aniline. Similar products are formed from azoxybenzene and benzene at 600° with a few exceptions; aniline is a major product and nitrobenzene, triphenylamine, and phenylcarbazoles are not produced. Studies with benzene-d_6 and cyclohexane at 600° showed that in the presence of benzene, nitrosobenzene dissociates to phenyl radical and NO. Disproportionation of nitrosobenzene to azoxybenzene and nitrobenzene occurs in the presence of cyclohexane at 600° but is minor in the presence of benzene.

Although nitrosobenzene and azoxybenzene have been the subject of many investigations, their behavior at elevated temperatures has been relatively unexplored. Bamberger[1] found that nitrosobenzene decomposed at 100° to give mainly azoxybenzene, together with small quantities of nitrobenzene, aniline, *o*-hydroxyazobenzene, and *o*- and *p*-hydroxyazoxybenzene. He proposed that the nitrosobenzene was converted to a mixture of phenylhydroxylamine and nitrobenzene, and the former reacted with nitrosobenzene to give azoxybenzene. Knipscheer[2] pyrolyzed azoxybenzene at 240–250° in the presence of carbon dioxide and obtained 2- and 4-hydroxyazobenzene and azobenzene as products. Dry distillation of azoxybenzene also gave azobenzene along with aniline and nitrosobenzene.[3]

To characterize further the thermal chemistry of nitrosobenzene, we examined its reactions with benzene, benzene-d_6, and cyclohexane. As nitrosobenzene readily gives azoxybenzene, the reactions of azoxybenzene were also studied.

Experimental Section

Experimental procedures and analyses have been described.[4] In a typical experiment, a solution of 19.8 g (0.1 mol) of azoxybenzene and 39 g (0.5 mol) of benzene was pumped into a Vycor tube filled with Vycor chips at 600° under a helium flow of 20 cc/min, with a contact time of 16.1 sec. The vapors were condensed in a flask at 0°; the condensate was distilled to give 32.4 g of benzene and 14.0 g of residue whose analysis is shown in Table II.

Results and Discussion

Nitrosobenzene and Azoxybenzene with Benzene.—The products from the reaction of nitrosobenzene with benzene at 200–600° are listed in Table I. Nitrosobenzene decomposes to nitrobenzene and azoxybenzene at 200–400°, whereas at 500–600° diphenylamine, biphenyl, and carbazoles are the major products. To

TABLE I

REACTION OF NITROSOBENZENE WITH BENZENE[a]

	Relative concentration[b]				
Products	200°	300°	400°	500°	600°
Nitrobenzene	19.1	19.3	17.5	7.1	5.9
Azoxybenzene	76.1	75.7	62.1		
Azobenzene	3.4	3.9	6.5		
Diphenylamine	Trace	0.6	8.2	33.0	34.3
Aminobiphenyls					0.7
Biphenyl			2.7	37.4	30.2
Phenol	1.2	0.5	1.0	8.4	10.1
Diphenyl ether, hydroxybiphenyls					3.6
Carbazole			1.0	1.4	1.2
Phenylcarbazoles			1.0	11.5	12.0
Triphenylamine				1.0	1.4
Aniline				Trace	0.6

[a] Reaction conditions: contact time, 10–19 sec; mole ratio nitrosobenzene:benzene = 1:5. [b] Determined by gas chromatography.

(1) E. Bamberger, *Ber.*, **35**, 1606 (1902).
(2) H. M. Knipscheer, *Recl. Trav. Chim. Pays-Bas*, **22**, 1 (1903).
(3) E. Bamberger, *Ber.*, **27**, 1182 (1894).
(4) E. K. Fields and S. Meyerson, *J. Org. Chem.*, **33**, 2315 (1968); **35**, 62 (1970).

ascertain the fate of azoxybenzene above 500°, we examined the reaction of azoxybenzene with benzene at 600°. A comparison of the products from this reaction with those of the corresponding nitrosobenzene reaction is shown in Table II. Both reactions gave similar products, with some noteworthy exceptions. Aniline was a major product in the azoxybenzene reaction, whereas only trace amounts were obtained from nitrosobenzene. Nitrobenzene and phenylcarbazoles were not observed in the azoxybenzene reaction, and the relative concentration of diphenylamine from this reaction was approximately one-third

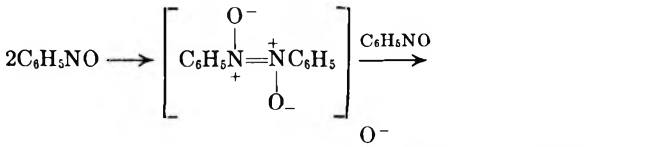
TABLE II

REACTION OF NITROSOBENZENE AND AZOXYBENZENE WITH BENZENE

Products	Relative concentration[a] Nitrosobenzene[b]	Azoxybenzene[c]
Diphenylamine	34.3	10.0
Aminobiphenyls	0.7	2.8
Biphenyl	30.2	33.8
Phenol	10.1	15.4
Diphenyl ether, hydroxybiphenyls	3.6	2.4
Carbazole	1.2	3.7
Phenylcarbazoles	12.0	
Azobenzene		1.9
Aniline	0.6	30.0
Nitrobenzene	5.9	
Triphenylamine	1.4	

[a] Determined by gas chromatography. [b] Conditions: 600°; contact time, 9.5 sec; mole ratio nitrosobenzene:benzene = 1:5. [c] Conditions: 600°; contact time, 16.1 sec; mole ratio azoxybenzene:benzene = 1:5.

less than that found in the corresponding nitrosobenzene reaction. The data in Tables I and II suggest that nitrosobenzene is reacting *via* two paths: (1) conversion to azoxybenzene and nitrobenzene followed by the decomposition of azoxybenzene, and (2) decomposition to a phenyl radical and NO. The latter reaction predominates above 400°. We also observed the thermal conversion of nitrosobenzene to azoxybenzene and nitrobenzene at 140–250° in the inlet system of the mass spectrometer.



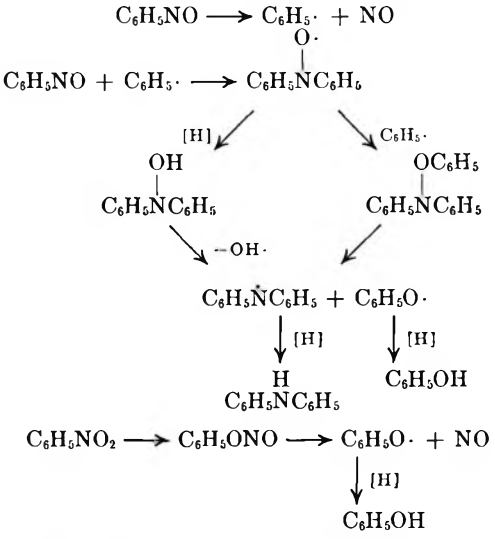
$$C_6H_5NO \longrightarrow C_6H_5\cdot + NO \quad (2)$$

Nitrosobenzene and Azoxybenzene with Benzene-d_6. —To determine the origin of the phenyl groups in phenol, biphenyl, and the amine products, as well as the partitioning of nitrosobenzene between its dissociation to phenyl radical and NO and its conversion to azoxybenzene, we examined the reaction of nitrosobenzene and azoxybenzene with benzene-d_6 at 600°. The isotopic distribution of the major products is shown in Tables III and IV. Contact times were short enough to avoid appreciable thermal scrambling of protium and deuterium,[5] as evidenced by the

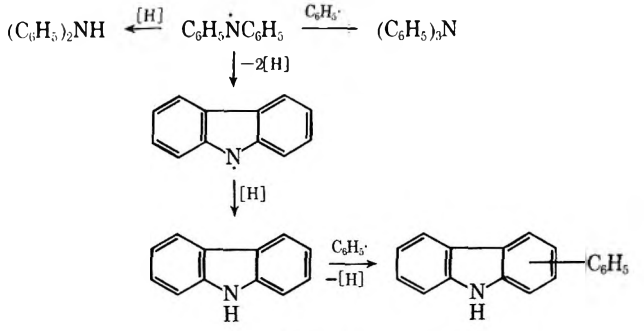
(5) E. K. Fields and S. Meyerson, *J. Amer. Chem. Soc.*, **82**, 21 (1966).

SCHEME I

Diphenylamine and Phenol



Phenylcarbazole, Carbazole, and Triphenylamine



Biphenyl

$$C_6H_5\cdot + C_6H_6 \xrightarrow{-[H]} C_6H_5C_6H_5$$

TABLE III

REACTION OF NITROSOBENZENE WITH BENZENE-d_6[a]

D atoms	Isotopic distribution of products: Benzene	Nitrobenzene	Phenol	Biphenyl	Diphenylamine	Carbazole	Phenylcarbazoles
0	0.5	96.1	82.9	2.8	74.7	77.5	77.3
1	0.5	3.9	12.3	1.4	17.1	12.5	15.2
2			1.6		1.5	1.5	2.2
3						1.5	
4	0.5		1.6	4.9	1.5	7.0	3.8
5	6.4		1.6	70.6	5.2		1.5
6	92.1			4.2			
7							
8							
9				2.1			
10				14.0			

[a] At 600°, contact time 10.4 sec; mole ratio nitrosobenzene:benzene = 1:5; isotopic composition of benzene, 0.2% d_4, 5.3% d_5, 94.5% d_6.

deuterium distribution of the recovered benzene. The isotopic distribution of nitrobenzene in Table III indicates that it was derived solely from nitrosobenzene, with the small amount of d_1 component apparently arising by protium–deuterium exchange. The amines, as well as phenol from both reactions, had similar deuterium distributions, chiefly d_0 and d_1 species, with only 5–9% of the diphenylamine and carbazoles arising from reactions involving benzene-d_6 and benzene-

TABLE IV

REACTION OF AZOXYBENZENE WITH BENZENE-d_6[a]

	Isotopic distribution of products							
D atoms	Benzene	Phenol	Aniline	Biphenyl	Diphenylamine	Aminobiphenyl	Azobenzene	Carbazole
0	3.1	89.6	86.2	15.2	77.5	71.9	100	74.9
1	0.7	8.5	12.7	4.9	13.3	12.9		13.7
2		0.5	0.8	0.8	1.3	3.5		2.7
3		0.5	0.3	0.2	0.3	0.6		2.5
4	0.5	0.5		4.8	1.1	1.2		6.3
5	7.4	0.4		56.8	5.9	8.8		
6	88.3			4.9	0.6	1.1		
7				0.4				
8				0.2				
9				1.7				
10				10.1				

[a] At 600°, contact time 16.2 sec; mole ratio azoxybenzene:benzene = 1:5; isotopic composition of benzene, 0.5% d_4, 5.8% d_5, 93.7% d_6.

TABLE V

REACTION OF NITROSOBENZENE AND AZOXYBENZENE WITH CYCLOHEXANE

	Relative concentration[d]	
Products[a]	Nitrosobenzene[b]	Azoxybenzene[c]
Diphenylamine	25.5	6.8
Aminobiphenyls	0.5	1.4
Biphenyl	6.9	9.1
Phenol	13.1	31.5
Diphenyl ether, hydroxybiphenyls	2.9	6.5
Nitrobenzene	5.0	1.7
Aniline	39.0	36.7
Carbazole	2.3	2.8
N-Phenylcarbazole	0.7	0.5
Azobenzene	3.3	3.0
Triphenylamine	0.8	

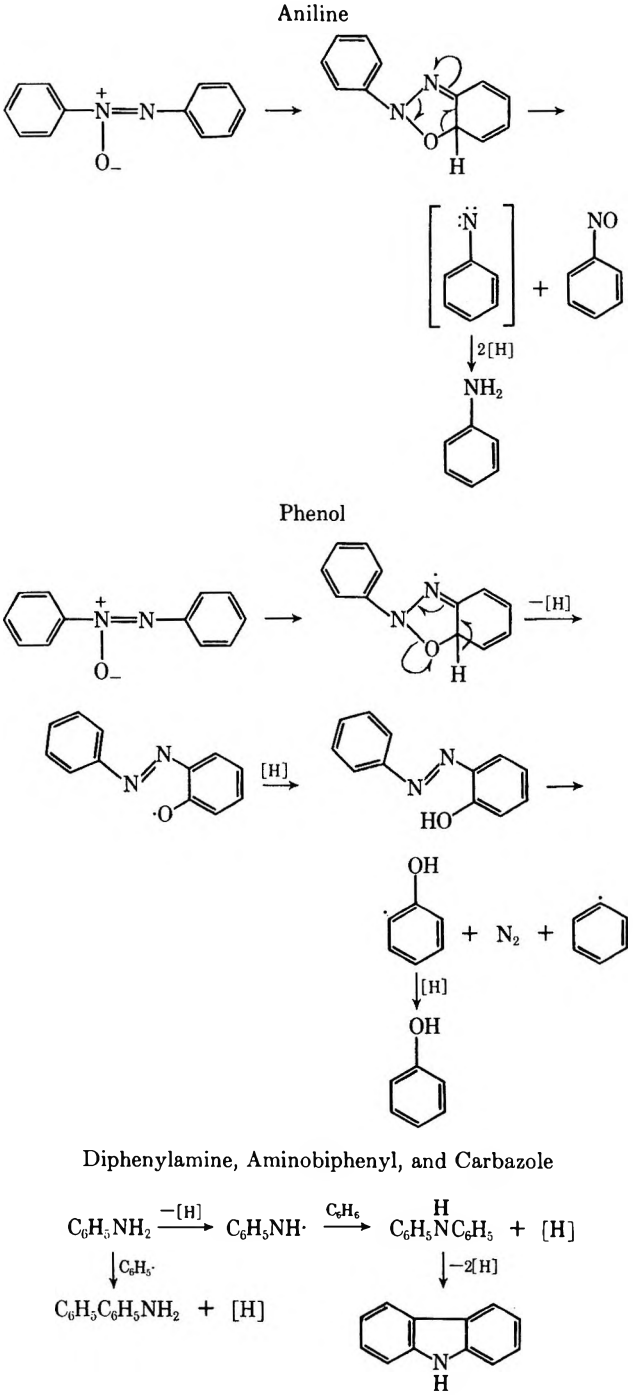
[a] The lower boiling products were benzene, cyclohexadiene, and cyclohexene. [b] At 600°, contact time 16.6 sec; mole ratio nitrosobenzene:cyclohexane = 1:2. [c] At 600°, contact time 20.2 sec; mole ratio azoxybenzene:cyclohexane = 1:4. [d] Determined by gas chromatography.

d_6-derived intermediates. Biphenyl from the nitrosobenzene reaction consisted largely of d_5 and d_{10} species with only 4.2% ($d_0 + d_1$) originating from nitrosobenzene, whereas biphenyl derived solely from azoxybenzene accounted for 20% ($d_0 + d_1$) of the total biphenyl. The deuterium distribution of aniline indicated that the aromatic ring was derived solely from azoxybenzene and that azoxybenzene was decomposing to an intermediate which had ready access to hydrogen. Reactions based on the data presented here are suggested in Schemes I and II to account for the major products derived from nitrosobenzene and azoxybenzene, respectively.

The difference in relative concentrations of aniline and diphenylamine derived from nitrosobenzene and azoxybenzene at 600°, as well as the isotopic distribution of the products from the benzene-d_6 reactions, show that nitrosobenzene dissociates to a phenyl radical and NO. Little nitrosobenzene goes to azoxybenzene above 400°. Nitrosobenzene acts as a trap for phenyl radicals, giving diphenylnitroxide.[6] As a result, less nitrosobenzene is available for conversion to azoxybenzene.

(6) G. R. Chalfont, D. H. Hey, K. S. Y. Liang, and M. J. Perkins, *Chem. Commun.*, 367 (1967); A. Mackor, Th. A. J. W. Wajer, Th. J. deBoer, and J. D. W. van Voorst, *Tetrahedron Lett.*, 2115 (1966).

SCHEME II



Nitrosobenzene and Azoxybenzene with Cyclohexane.—To gain additional information concerning the decomposition of nitrosobenzene to phenyl radical and NO and its conversion to azoxybenzene, we carried out the reactions of nitrosobenzene and azoxybenzene with cyclohexane at 600°. As phenyl radical prefers to abstract hydrogen from cyclohexane rather than add to the aromatic ring of benzene at 600°,[7] some of the phenyl radicals generated from nitrosobenzene should be converted to benzene. This should facilitate the conversion of nitrosobenzene to azoxybenzene and its subsequent decomposition to aniline. The data from these reactions are shown in Table V. Aniline indeed was formed as a major product from nitrosobenzene; product distributions from both nitrosobenzene and azoxybenzene with cyclohexane were more nearly the same than those from the corresponding reactions with benzene.

This study shows that the thermal chemistry of nitrosobenzene is quite complex. Dissociation of nitrosobenzene to azoxybenzene and nitrobenzene or to phenyl radicals and NO depends on temperature and the nature of the hydrocarbon used as a reagent.

(7) A. I. Feinstein, E. K. Fields, and S. Meyerson, *J. Org. Chem.*, **35**, 303 (1970).

Registry No.—Nitrosobenzene, 586-96-9; azoxybenzene, 495-48-7; benzene, 71-43-2; benzene-d_6, 1076-43-3; cyclohexane, 110-82-7.

Acknowledgment.—We acknowledge with thanks the assistance of S. Meyerson of Standard Oil of Indiana and D. K. Albert of the American Oil Company for mass spectrometric and gas chromatographic analyses.

The Basic Hydrolysis of Solubilized Octane-2-diazotate. Dissection of Conservation and Exchange Pathways[1,2]

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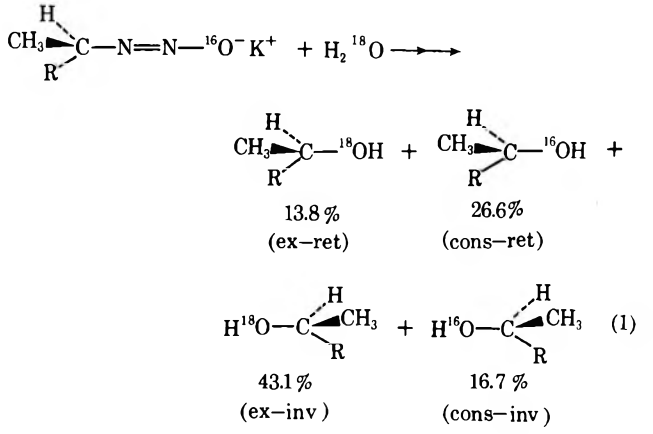
Received May 13, 1971

Solubilized optically active octane-2-diazotate (^{16}O) in hexamethylphosphoric triamide–dicyclohexyl-18-crown-6 was hydrolyzed by slow addition to $H_2{}^{18}O$. The resultant 2-octanol was attributed to four product-forming pathways: ^{18}O-incorporation–retention, 18.9%; ^{18}O-incorporation–inversion, 58.5%; ^{16}O-conservation–retention, 16.5%; ^{16}O-conservation–inversion, 6.0%. The results are compared to those obtained upon direct addition of $H_2{}^{18}O$ to solid octane-2-diazotate; mechanisms are discussed.

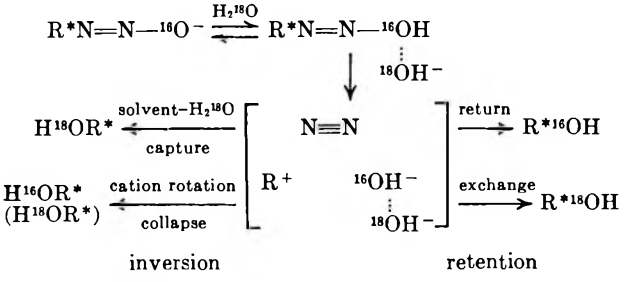
We have analyzed the hydrolysis of optically active potassium octane-2-diazotate (I) with $H_2{}^{18}O$, a reaction which gave the results summarized in eq 1, R = n-C_6H_{13}.[4,5]



Solvent incorporating (exchange) inversion was the predominant pathway (ex–inv product), but substantial conservation of the original diazotate oxygen was also observed. The exchange pathways afforded 2-octanol with 76% overall *inversion*, whereas the conservation pathways afforded 2-octanol with 61% overall *retention*. This pattern, exchange with inversion and conservation with retention, was also observed in the ethanolysis of potassium 1-phenylethanediazotate.[2]

We proposed[4] a mechanism in which $H_2{}^{18}O$ and $^{16}OH^-$ competed for 2-octyl cation in a nonsymmetrically hydrated ion pair (see Scheme I). This mechanism

SCHEME I



was an adaptation of White's "counterion hypothesis," which has worked well for deaminative processes in nonaqueous solvents.[6]

The previous hydrolyses of I[4,5] involved the addition of water to the solid salt. The ensuing reactions were very rapid on the normal time scale, and the results could have reflected local inhomogeneities in the reac-

(1) Alkyl Diazotates. IX.[2]

(2) Part VIII: R. A. Moss and M. J. Landon, *J. Amer. Chem. Soc.*, **92**, 5755 (1970).

(3) (a) Fellow of the Alfred P. Sloan Foundation; to whom correspondence should be addressed at Rutgers University. (b) National Science Foundation Undergraduate Research Participant, summer 1970. (c) Colgate-Palmolive Research Center.

(4) R. A. Moss, D. W. Reger, and E. M. Emery, *J. Amer. Chem. Soc.*, **92**, 1366 (1970).

(5) R. A. Moss and S. M. Lane, *ibid.*, **89**, 5655 (1967).

(6) E. H. White and D. J. Woodcock in "The Chemistry of the Amino Group," S. Patai, Ed., Interscience, New York, N. Y., 1968, pp 440–483. This excellent review includes a definitive statement of the "counterion hypothesis," as well as elegant illustrations of its applicability.

tant system, particularly if the rate of decomposition of protonated I were comparable to the rate of solution and hydration of I. That is, bimolecular reactions of octane-2-diazotic acid (or ion pairs derived therefrom), in local, abnormally high concentrations could have accounted for some of the cons–inv product of eq 1. It seemed unlikely that such reactions occurred between truly dissolved, solution-equilibrated octane-2-diazotic acid, because the stereochemical outcome of the overall reaction was not sensitive to the addition of such strong nucleophiles as hydroxide and azide.[5]

To gain perspective on this problem, we have prepared apparent solutions of I in hexamethylphosphoric triamide (HMPT) containing the macrocyclic polyether, dicyclohexyl-18-crown-6.[7] "Inverse" hydrolyses of I were carried out by slow addition of these solutions to water. Here we present the results of these studies, which refine and extend our earlier work.[4,5]

Results

Stereochemistry.—A clear, dark orange solution of optically active I[4,5] in HMPT[8] was decomposed by slow addition to a large excess of vigorously stirred water (200 ml). Nitrogen evolution was 87% of the theoretical quantity. The gc-isolated 2-octanol product was converted to a mixture of diastereomeric *d*- and *l*-2-octyl L-acetyllactate esters,[4] which was assayed by gc.[9] The analysis indicated that the 2-octanol had been 30.02% optically pure *d* enantiomer. Since the original I derived from *l*-2-octylamine of 95% optical purity, the overall stereochemical result for I → 2-octanol was 31.6% net inversion. A second, analogous experiment gave a stereochemical result of 31.2% net inversion.[10]

These results should be compared with those for the direct addition of water to solid I, in which 20% net inversion was found.[4,5] (For a discussion of errors in the stereochemical data, see the Experimental Section.)

Oxygen Conservation.—A solution of 0.61 mmol of I in 5 ml of HMPT, containing also 1.58 mmol of the crown ether[7] and 0.82 mmol of potassium *tert*-butoxide, was slowly added to 2.5 ml of water which was 20.82 atom % ^{18}O (D normalized), with the evolution of 88% of the theoretical amount of nitrogen.

Mass spectral examination of the isolated 2-octanol revealed 14.83 atom % ^{18}O, which indicated that the I → 2-octanol conversion had occurred with 29% of ^{16}O (original oxygen) conservation. A duplicate experiment gave 2-octanol containing 15.74 atom % ^{18}O, indicative of 24% ^{16}O conservation.

These results are to be contrasted to those for the direct addition of $H_2{}^{18}O$ to solid I, in which *ca.* 40% of ^{16}O conservation was observed.[4,5]

Stereochemical Dissection of Oxygen Conservation and Exchange.—The above experiments demonstrated that the I–HMPT inverse hydrolysis occurred with somewhat more overall inversion and less ^{16}O conservation than did the direct addition of water to I. In order to obtain a clearer picture of the origins of these overall changes, we hydrolyzed optically active I–HMPT with $H_2{}^{18}O$, converted the isolated 2-octanol to the diastereomeric 2-octyl L-acetyllactate esters, and determined the $^{16}O/^{18}O$ ratio of each ester. A display of the results is given in Table I.

TABLE I

2-OCTANOL FROM THE INVERSE HYDROLYSIS OF HMPT-DISSOLVED OPTICALLY ACTIVE I WITH $H_2{}^{18}O$[a]

Σ ^{18}O in ROH, atom %		Stereochemistry (gc)		Atom % ^{18}O in resolved ROH	
Found	Calcd	Retained 2-octanol, %	Inverted 2-octanol, %	*l*-ROH (retention)	*d*-ROH (inversion)
15.21[b]	16.07	36.35	63.65	11.46[c]	18.70[c-e]

[a] Conditions: 5.83 mmol of I (derived from *l*-2-octylurethane[4,5] of 94% optical purity) in 10 ml of HMPT, containing 12.9 mmol of the crown ether[7] and 6.1 mmol of potassium *tert*-butoxide, was added to 5 ml of $H_2{}^{18}O$ (20.82 atom % ^{18}O, D normalized). [b] Measured directly on the isolated 2-octanol, before its conversion to the L-acetyllactates. [c] Measured on the appropriate 2-octyl L-acetyllactate. [d] Dilution of the ^{18}O pool by ^{16}O exchanged from I could have lowered the effective average ^{18}O by no more than 0.3 atom %. [e] We estimate all reading errors for mass spectral data to be less than 1%.

The (gc) stereochemical data for this run correspond to a stereochemical course of 29% net inversion for the I → 2-octanol conversion, in reasonable agreement with the 31.4% (average) result (above). However, this determination was less precise than the former cases; see the Experimental Section. The overall ^{18}O incorporation observed in the unresolved 2-octanol, 15.21 atom %, agrees well with the 15.28 atom % (average) ^{18}O incorporation (above). The deviation of *back-calculated* total ^{18}O in the unresolved 2-octanol from the observed value (5.7% deviation) is somewhat larger than in our previous work.[4] In particular, we consider the ^{18}O analyses of the octyl L-acetyllactates to be more accurate than the ^{18}O analyses of 2-octanol. With the esters, there is no interference between ^{16}O and ^{18}O analogous ions; this is a minor problem in the 2-octanol analyses in the *m/e* 43, 45, 47 series. Moreover, the 2-octanol is sensitive to oxidation, which affords 2-octanone, complicating the analysis. The esters are not subject to this problem. Since the mechanistic analysis of the present experiment (see below) uses only the $^{18}O/^{16}O$ data determined on the esters, we feel that the isotope distribution data of Table I are acceptable. Further remarks about the mass spectral analyses can be found in the Experimental Section.

The data of Table I can be processed[4] to permit the construction of Table II, in which a percentage is assigned to each of the four octanol-forming pathways summarized in eq 1. A correction was made for the 6% of racemic I which had been present, and which contributed 2.2% to the 2-octanol enantiomers formed with ^{18}O exchange and 0.8% to the 2-octanol enantiomers formed with ^{16}O conservation (based on total octanol = 100%, and on the results of the $H_2{}^{18}O$ hydrolyses of racemic I, above). Table II also includes analogous results for the direct addition of $H_2{}^{18}O$ to solid, optically active I.[4]

(7) C. J. Pedersen, *J. Amer. Chem. Soc.*, **89**, 7017 (1967).

(8) 3.04 mmol in 25 ml of HMPT. Also present were 7.10 mmol of the crown ether[7] and 3.11 mmol of potassium *tert*-butoxide.

(9) E. Gil-Av, R. Charles-Sigler, G. Fischer, and D. Nurok, *J. Gas Chromatogr.*, **4**, 51 (1966); H. C. Rose, R. L. Stern, and B. L. Karger, *Anal. Chem.*, **38**, 469 (1966).

(10) A control experiment, in which I–HMPT–crown ether was added to D_2O, gave 2-octanol with only 0.5% of one carbon-bound D (mass spectrum). The importance of 2-diazooctane as a 2-octanol precursor was therefore negligible. It is of greater importance in the direct additions (up to 8%).[4,5]

TABLE II

STEREOCHEMISTRY OF EXCHANGE AND CONSERVATION PATHWAYS IN OCTANE-2-DIAZOTATE → 2-OCTANOL

Run	Σ^{18}O exchange[a,b]	Stereochemistry[a,c] Ret	Stereochemistry[a,c] Inv	Σ^{16}O conservation[a,b]	Stereochemistry[a,c] Ret	Stereochemistry[a,c] Inv
Direct addition[d]	58.4	13.8	43.1	41.6	26.6	16.7
HMPT–I inverse[e]	73.0	18.9	58.5	27.0	16.5	6.0[f]

[a] Per cent of total 2-octanol product. [b] Calculated from atom % ^{18}O (^{16}O) in the unresolved 2-octanol. [c] Calculated from the atom % ^{18}O (^{16}O) in the 2-octyl acetyllactates. That, *e.g.*, (13.8 + 43.1) ≠ 58.4, indicates the "give" in the data, since the two sides of the inequality were derived from independent experimental measurements. The agreement is less satisfactory in the second run (see above). [d] $H_2{}^{18}O$ added to solid I, ref 4. [e] HMPT–I–crown ether added to $H_2{}^{18}O$, this work. [f] A discussion of probable error in these data can be found in the Experimental Section.

Discussion

The HMPT–I inverse addition procedure enhances *both* the ex–ret and ex–inv pathways (eq 1), as compared to the "direct" hydrolysis procedure. However, both exchange pathways are augmented in proportion, and the overall stereochemistry of this pathway remains constant (*ca.* 76% inversion, 24% retention). The overall contribution of exchange or solvent incorporating pathways increases from 58% (direct addition) to 73% (inverse addition).

In contrast, *both* ^{16}O conservation pathways, cons–ret and cons–inv (eq 1), are suppressed in the inverse addition. The latter is most strongly affected, and, as a result, the stereochemistry of the ^{16}O conservation pathway changes from 61% retention, 39% inversion (direct addition) to 73% retention, 27% inversion (inverse addition).

Although the stereochemistry of the exchange process did not change, whereas the stereochemistry of the conservation process moved toward greater retention, the increased importance of the total exchange process is the dominant factor in determining the *overall* stereochemical change, which therefore moves from *ca.* 20% (direct addition) to *ca.* 30% *net* inversion (inverse addition).

The competitive processes which afford the products of eq 1 have been discussed in terms of Scheme I,[4] in which the cons–inv product was pictured as arising from cation rotation within the ion pair followed by collapse.[6] It is precisely this product, however, which is most dramatically suppressed on changing the experimental procedure from direct to inverse addition. It is therefore tempting to conclude that a significant portion of this product arose *via* bimolecular reactions of (^{16}O) octane-2-diazotic acid (or of $^{16}OH^-$ and octane-2-diazotic acid) present in local, abnormally high concentrations during the addition of water to solid I. These pathways should mainly yield cons–inv 2-octanol, and ought to decrease in importance when HMPT–I is slowly added to water.[11]

Bimolecular, inverting displacements by nucleophiles on RN=NX (X = OH, halide, –OOCR′) are not common, but they are not unknown. They certainly contribute in the decomposition of RN=NX (R = *sec*-alkyl) in poor solvents such as pentane.[6,12] We have also observed this type of reaction in the ethereal acetylation of butane-2-diazotate.[13]

Interestingly, White observed that "in the decomposition of the nitrosoamide of 1-phenylethylamine in which a benzylic cation is formed, the displacement could not be detected. . . ."[6,12] In this light, and in contrast to the present results for the hydrolysis of I, we recall our study of the ethanolysis of optically active 1-phenylethane-1-diazotate, in which the conservation product (1-phenylethanol) formed with *ca.* 73% net retention and the exchange product (1-phenylethyl ethyl ether) formed with *ca.* 30% net inversion.[2] These stereochemical results, for a reaction which most likely involved a benzylic cation, were essentially independent of experimental procedure, whether ethanol was added to the solid diazotate or a solution of the diazotate in HMPT–crown ether was added to ethanol.[2]

Assuming, then, that the present experiments with HMPT–I have obviated bimolecular reactions of octane-2-diazotic acid, the results, fitted to Scheme I, can be compared to other, related work. For example, conservation pathways in the acetolysis of *N*-(1-phenylethyl)-*N*-nitroso-2-naphthamide led to 1-phenylethyl 2-naphthoate with 81% retention and 19% inversion.[14] Compare with 73% retention and 27% inversion for the ^{16}O conservation pathways in the HMPT inverse hydrolysis of I (above). In contrast, however, exchange pathways in the former reaction led to 1-phenylethyl acetate with 56% retention and 44% inversion. This net retention is markedly different from the 76% inversion, 24% retention which characterizes the ^{18}O exchange pathways in the hydrolysis of I. The variance of stereochemical course in the exchange pathways of the two reactions can be understood in terms of (1) the much greater medium nucleophilicity in the hydrolysis of I, (2) the inferior stability of the 2-octyl cation, and (3) greater competitive ability of front-side (retention) exchange processes[6] (acetate for 2-naphthoate) in the less nucleophilic medium of the nitrosoamide decomposition.

These factors would combine to favor greater inverting displacement in the basic hydrolysis of I, as opposed to the acetolysis of *N*-(1-phenylethyl)-*N*-nitroso-2-naphthamide (*i.e.*, of 1-phenylethyl diazo-2-naphthoate).

A search of the literature reveals that the stereochemical aspects of the conservation process, as now determined in the inverse HMPT–I hydrolysis, are similar to those of other conservation processes which involve different alkyl groups, gegenions, and solvents; see Table III. Indeed, this remarkable resemblance, maintained over a diversity of reactants, suggests both the fundamentality of the processes being examined, and that the inverse HMPT–I hydrolysis has probably obviated most of the bimolecular reactions of octane-2-diazotic acid.

Finally, we note the possibility that the change from direct to inverse hydrolysis of I may not have eliminated

(11) In the presence of an ethereal phase, the *direct* hydrolysis of solid I affords *ca.* 21% cons–inv 2-octanol, but only 15% cons–ret 2-octanol. This net inversion in the conservation process has been tentatively attributed to "bimolecular displacement reactions occurring with inversion (and ^{16}O conservation), possibly between RN=N–^{16}OH molecules extracted into the organic phase."[4]

(12) E. H. White, *J. Amer. Chem. Soc.*, **77**, 6014 (1955).

(13) R. A. Moss and K. M. Luchter, *J. Org. Chem.*, in press.

(14) E. H. White and C. A. Aufdermarsh, Jr., *J. Amer. Chem. Soc.*, **83**, 1179 (1961).

TABLE III
STEREOCHEMISTRY OF THE CONSERVATION PATHWAYS OF SOME DEAMINATIVE REACTIONS

$$RN{=}NX \xrightarrow{\text{solvent}} N_2 + RX$$

R	X	Solvent	% retention	% inversion	Ref
$C_6H_5CHCH_3$	$OOCC_{10}H_7$	CH_3COOH	81	19	*a*
$C_6H_5CHCH_3$	OH	CH_3COOH	79	21	*b*
$C_6H_5CHCH_3$	OH	C_2H_5OH	87	13	*c*
$C_6H_5CHCH_3$	OC_2H_5	CH_2Cl_2	82	18	*c*
$C_2H_5CHCH_3$	OOC_6H_5	CH_3COOH	68	32	*d*
		Compared to			
$C_6H_{13}CHCH_3$	^{16}OH	HMPA-$H_2{}^{18}O$	73	27	*e*

[a] Reference 14. [b] R. Huisgen and C. Rüchardt, *Ann.*, 601, 21 (1956). [c] Reference 2. [d] Reference 12. [e] This work.

all bimolecular reactions of octane-2-diazotic acid, and that some of the 6% of cons–inv 2-octanol still arises in this way. On the face of it, this seems unlikely, because the experimental procedure maintains a low concentration of the diazotic acid during its decomposition.

It could be argued that decomposition of protonated I is so rapid that it competes with the diffusive processes which equilibrate each drop of HMPT–I newly added to the water. Again, we doubt this. But, if the point is pressed, a curious logical impasse develops. If protonated I is held not to have been equilibrated before significant decomposition occurred, then neither can the HMPT be said to have dispersed. In view of the basic and nucleophile-potentiating character of HMPT,[15] the observed decrease in cons–inv 2-octanol might then be revealing less about possible bimolecular reactions of octane 2-diazotic acid during "direct" addition, than about a specific HMPT solvent effect during "inverse" addition. Indeed, we cannot completely rule out the possibility that a general HMPT solvent effect is at least partly responsible for the diminution in cons–inv 2-octanol. For, in the inverse addition, optically active I–$H_2{}^{18}O$ experiment, we were forced to use conditions which gave a *final* HMPT/H_2O mole ratio of ~0.2.

A referee has suggested that "a temperature effect may also be involved in view of the exothermic reaction that results on addition of water to the diazotate." It is true that temperature cannot be so easily controlled during the "direct" as opposed to the "inverse" hydrolysis. However, we suspect that the "exothermicity effect" is likely to be small, because a deliberate 40° temperature variation has only a small effect on the stereochemistry of the diazotate decomposition.[5] Moreover, the direct hydrolysis[4] was carried out at −20°, to allow for the exothermicity of the reaction; the inverse hydrolysis was done at 0°.

In conclusion, although the four pathways which, *via* Scheme I, lead to the four 2-octanols of eq 1, might be somewhat redistributed in other solvent systems, it seems likely that none would disappear entirely, and that their competition, an example of the deaminative counterion hypothesis,[6] is as germane in aqueous as it is in nonaqueous solvent systems.

Experimental Section

Stereochemical Runs.—Optically active octane-2-diazotate (potassium) (prepared from *l*-2-octylamine of 95% optical purity) was made as previously described.[4,5] A typical experiment, commencing with the optically active *N*-nitroso-*N*-2-octylurethane,[4,5] is described in order to illustrate how the HMPT–I solutions were prepared.

Potassium *tert*-butoxide (0.69 g, 6.15 mmol) was placed in a dry, nitrogen-filled, 50-ml, three-neck flask. After the addition of 11 ml of dry ether, the contents of the flask was magnetically stirred and cooled to −30°. A solution of 0.70 g (3.04 mmol) of optically active *N*-nitroso-*N*-2-octylurethane in 11 ml of dry ether was injected through a septum. The solution was stirred for 45 min at −30 to −20°. No gas evolution was observed. At the end of this period, the solvent was removed with a mechanical pump; the temperature was allowed to rise to *ca.* 25° during "drying."

A solution of 2.64 g (7.10 mmol) of dicyclohexyl-18-crown-6[7] (Du Pont Co., purified grade) in 25 ml of HMPT (distilled from CaH_2) was injected, and stirring produced a clear orange solution within 10 min. The solution was transferred by syringe to an addition funnel and then added, with stirring, over 30 min, to 200 ml of water at 0°. The reaction vessel was connected to a gas buret, and 87% of the theoretical gas evolution was observed during the addition process.

The product mixture was extracted with 150 ml of ether and then with four 100-ml portions of ether. The combined ethereal extracts were backwashed with water (two 100-ml portions), and then allowed to stand over $MgSO_4$ for 12 hr. Filtration and removal of solvent (rotary evaporator) gave 3.54 g of an oil, from which 55 μl of 2-octanol was isolated by iterative gc on a 5 ft × 0.25 in., 5% Carbowax on 45/60 Gas-Chrom P column. The operating conditions follow: injector, 215°; column, 90°; detector, 210°; helium head pressure, 20 psig.

After conversion of the 2-octanol to its L-acetyllactate diastereomers,[4] final analysis was carried out by gc on a 24 ft × 0.25 in., 10% 1,2,3-tris(2-cyanoethoxy)propane on 45/60 Gas-Chrom R column. The operating conditions follow: injector, 260°; column, 160°; detector, 240°; helium head pressure, 30 psig. Integration of the diastereomer peaks was by cut-and-weigh of Xerox copies of the original trace. Four copies were used for each trace, and three traces were obtained. The overall optical purity thus determined for the isolated 2-octanol was 30.02 ± 1.13%.[16] The diastereomer derived from *d*-2-octanol predominated. Taking account of the 95% optical purity of the initial amine, the stereochemical result was 31.6% net inversion.

A duplicate experiment gave 29.70 ± 0.97%[16] optically pure *d*-2-octanol, or 31.2% net inversion.

$H_2{}^{18}O$ Runs.—A similar procedure was used to prepare a solution of 0.61 mmol of racemic octane-2-diazotate in 5 ml of HMPT and 0.59 g (1.58 mmol) of the crown ether. This solution was slowly injected into 2.5 ml of Miles Laboratories' 20.82 atom % ^{18}O, D-normalized water. The precautions used in handling this water are discussed in our previous work.[4,5]

Nitrogen evolution was 88% of theory. The product mixture was poured into 50 ml of ether; the ether layer was separated and allowed to stand over $MgSO_4$ for at least 12 hr.[10] 2-Octanol was isolated by gc[17] of the (stripped) product mixture. Mass spectral analysis for $^{16}O/^{18}O$ on a consolidated Model 21-104 instrument, equipped with an electron multiplier, employed (principally) *m/e* 45 and 47. Corrections for natural heavy isotope abundances were made, based on the fragmentation pattern of the normal compound. There was 14.83 atom % of ^{18}O in the product 2-octanol. A second experiment afforded 2-octanol containing 15.74 atom % of ^{18}O.

Stereochemical ^{18}O Exchange Run.—This run was carried out as before, using 94% optically pure octane 2-diazotate and water which was 20.82 atom % ^{18}O, D normalized. Details appear in Table I.

The derived *d*- and *l*-2-octyl-L-acetyllactates were isolated by gc on the tris(2-cyanoethoxy)propane column and analyzed for $^{16}O/^{18}O$ by mass spectroscopy. Ions *m/e* 133 and 135[18] were principally employed. Corrections were made, based on the fragmentation pattern of the normal esters. The ester derived from *d*-2-octanol contained, per oxygen atom, 18.70 atom % ^{18}O. The ester derived from *l*-2-octanol contained 11.46 atom % ^{18}O.

(15) H. Normant, *Russ. Chem. Rev.*, **39**, 457 (1970); A. J. Parker, *Chem. Rev.*, **69**, 1 (1969).

(16) This error is the average deviation from the mean value of optical purity of the three gc traces. Within the analysis of each trace, deviation from the mean value of optical purity was smaller, *ca.* ±0.6%.

(17) On a 7 ft × 0.25 in. 5% Carbowax on 80/100 Chromosorb P column, 105°.

(18) These ions correspond to protonated acetyllactic acid: F. W. McLafferty, "Interpretation of Mass Spectra," W. A. Benjamin, New York, N. Y., 1967, p 137.

In contrast to our previous experience in determining 2-octanol optical purity by the gc-diastereomer method, the results in this run were imprecise. Thus, although the Xerox cut-outs of each of three traces were mutually consistent (four copies per trace, average deviations 1.30, 1.71, 1.13%), the final (uncorrected) optical purities obtained were 22.24, 32.72, and 26.94%. The average value was 27.30 ± 3.61%. The stereochemical course of the reaction was therefore 27.30/0.94 ~ 29% net inversion.

Although we cannot account for the poor precision in this stereochemical determination, we can show that the results in Table II, which partly rest upon this determination, are relatively unaffected. Thus, using the lower, uncorrected, net inversion limit of (27.30 − 3.61) = 23.69%, we calculate a final 2-octanol distribution of ex-ret, 20.00; ex-inv, 56.74; cons-ret, 17.40; and cons-inv, 5.85%. The final values corresponding to the higher, uncorrected, net inversion of 30.91% afford a distribution of 17.88, 60.21, 14.73, and 6.23%, respectively. These limiting values are very similar to the distribution shown in Table II, which is based on the average, uncorrected, net inversion of 27.30%.

Registry No.—I, 27850-48-2.

Acknowledgments.—We are grateful to the National Science Foundation (GP-12645) and to the National Institutes of Health (GM-13585) for financial support. A. W. F. thanks the National Science Foundation (GY-7556) for summer support. We also thank the Colgate-Palmolive Co. for making available its mass spectroscopy facilities, and Professor D. Denney for a helpful discussion.

Reactions of Diazo Compounds with Tetrasubstituted 1,3-Cyclobutanediones and the Corresponding Dithiones. Isolation of Bis-Δ^3-1,3,4-thiadiazolines from the Dipolar Addition of Diazomethane to the Dithiones and Their Thermal Decomposition into Diepisulfides

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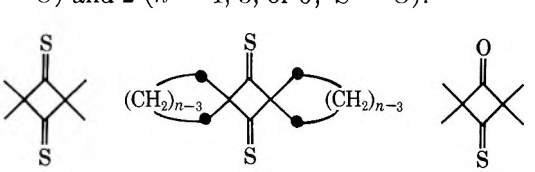
Received June 17, 1971

Tetramethyl-1,3-cyclobutanedithione (**1**), dispiro[4.1.4.1]dodecane-6,12-dithione (**2**, n = 5), and dispiro-[5.1.5.1]tetradecane-7,14-dithione (**2**, n = 6) on treatment with diazomethane at 0° lead to novel stereoisomeric bis-Δ^3-1,3,4-thiadiazolines **12**, **13** (n = 5), and **13** (n = 6), respectively. These bis adducts are reasonably stable and on thermolysis readily undergo loss of nitrogen to yield stereoisomeric mixtures of diepisulfides **17**, **18** (n = 5), and **18** (n = 6). Treatment of **1** with diphenyldiazomethane leads to the cis and trans diepisulfides **21**. Treatment of the diones **1** (S = O) and **2** (n = 4, 5, or 6; S = O) with ethanolic-ethereal diazomethane leads to the ring-expanded diones **22** and **23** (n = 4, 5, or 6), respectively. The relative ease of ring expansion stands in the order: **2** (n = 4; S = O) >>>> **2** (n = 5; S = O) > **1** (S = O) > **2** (n = 6; S = O). The possible reasons for this order are discussed.

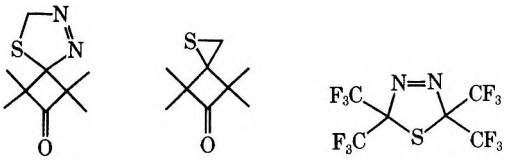
As part of a program designed to contrast the chemistry of –C=O and –C=S linkages, we have recently begun a study of various reactions of tetrasubstituted 1,3-cyclobutanedithiones **1** and **2** (n = 5 or 6) and the corresponding diones **1** (S = O) and **2** (n = 4, 5, or 6; S = O). This report deals with the reaction of diazomethane with dithiones **1** and **2** (n = 5 or 6) and diones **1** (S = O) and **2** (n = 4, 5, or 6; S = O).



1 **2** **3**

In general most simple aliphatic and alicyclic thiones are unstable in the monomeric state.[3] As a consequence, their chemistry and reactivity have not been fully investigated. The dithiones **1**[4] and **2** (n = 6)[5] and the monothione **3**[4a] have been prepared recently and join the ranks of such non-enethiolizable thiones as thiocamphor,[6] thiofenchone,[7] and adamantanethione[8] in possessing stable thione groups. Hexafluorothioacetone has been reported to undergo dimerization on standing for several hours.[9]

The reaction of several aliphatic thioketones with diazomethane (0°, ether) led to the corresponding episulfides along with methylthioalkenes (from the enethiol). In the case of diisopropyl thioketone only the episulfide was formed; in none of the cases was any thiadiazoline intermediate isolated.[10] Recently the reaction of **3** has been reported to lead to the unstable Δ^3-1,3,4-thiadiazoline **4** (tentatively characterized by ir and nmr spectroscopy).[11] The thiadiazoline **4** readily loses nitrogen to yield the episulfide **5**. Bis-



4 **5** **6**

(1) Fellow of the Humphrey Chemical Co., North Haven, Conn.

(2) Ethiopian Fellow of the African Graduate Fellowship Program (AFGRAD).

(3) (a) For a review see R. Mayer, J. Morgenstern, and J. Fabian, *Angew. Chem., Int. Ed. Engl.*, **3**, 277 (1964); (b) R. Mayer in "Organosulfur Chemistry," M. J. Janssen, Ed., Interscience. New York, N. Y., 1967, p 219; (c) R. Mayer and S. Bleisch, *Chem. Ber.*, **100**, 93 (1967); (d) E. Campaigne in "The Chemistry of the Carbonyl Group," S. Patai, Ed., Interscience, New York, N. Y., 1966, p 917; (e) M. Demuynck and J. Vialle, *Bull. Soc. Chim. Fr.*, 2748 (1967).

(4) (a) E. U. Elam and H. E. Davis, *J. Org. Chem.*, **32**, 1562 (1967). (b) R. D. Lipscomb (to E. I. du Pont de Nemours and Co., Inc.), U. S. Patent 3,297,767 (Jan 10, 1967); *Chem. Abstr.*, **66**, 65180r (1967).

(5) E. U. Elam (to Eastman Kodak Co.), British Patent 1,137,377 (Dec 18, 1968); *Chem. Abstr.*, **70**, 96253d (1969).

(6) D. C. Sen, *J. Indian Chem. Soc.*, **12**, 647 (1935).

(7) (a) D. C. Sen, *ibid.*, **14**, 214 (1937); (b) C. N. R. Rao and R. Venkataraghavan, *Spectrochim. Acta*, **18**, 541 (1962).

(8) (a) J. W. Greidanus and W. J. Schwalm, *Can. J. Chem.*, **47**, 3715 (1969); (b) J. W. Greidanus, *ibid.*, **48**, 3530, 3593 (1970).

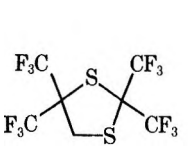
(9) (a) W. J. Middleton, E. G. Howard, and W. H. Sharkey, *J. Org. Chem.*, **30**, 1375 (1965); (b) W. J. Middleton, *ibid.*, **34**, 3201 (1969).

(10) D. Paquer and J. Vialle, *Bull. Soc. Chim. Fr.*, 3327 (1969).

(11) C. E. Diebert, *J. Org. Chem.*, **35**, 1501 (1970).

(trifluoromethyl)diazomethane reacts with hexafluorothioacetone to yield the Δ^3-1,3,4-thiadiazoline **6**, which is stable at room temperature and on thermolysis yields the corresponding episulfide.[9b]

Treatment of hexafluorothioacetone with diazomethane yields 1,3-dithiolane **7**.[12] Schönberg and coworkers have described reactions between diazoalkanes and several diaryl thioketones and have isolated either 1,3-dithiolanes **8** or episulfides **9** (R_2 and R_3 from the diazoalkane).[13]



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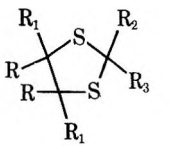

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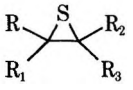
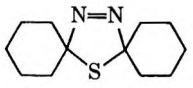


9

A synthetic route to Δ^3-1,3,4-thiadiazolines has recently been developed which involves dehydrogenation of 1,3,4-thiadiazolidines.[14] The Δ^3-1,3,4-thiadiazolines **10**,[14a,c] **11** (R = R_2 = *tert*-Bu, R_1 = H),[14b] **11** (R = R_1 = Et; R_2 = H),[14a,b] and **11** (R = R_2 = Et; R_1 = H)[14a,b] have been prepared, the latter two compounds being isolated at −10°. The thermolysis of these thiadiazolines led to the corresponding episulfides. The thiadiazoline **10** is the first reported example of an exceptionally stable system of this structure, mp 80° (without decomposition).[14a,c]



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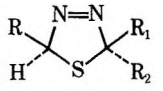

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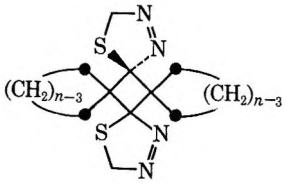
12



13

Results and Discussion

Reaction of the 1,3-Dithiones with Diazomethane. — Tetramethyl-1,3-cyclobutanedithione (**1**),[4] dispiro[5.1.5.1]tetradecane-7,14-dithione (**2**, n = 6),[5] and dispiro[4.1.4.1]dodecane-6,12-dithione (**2**, n = 5) were prepared in excellent yields by treatment of the corresponding diones with H_2S in the presence of HCl and zinc chloride in a cold methanol solution.[4b] The three dithiones are pleasant smelling, red-colored compounds which can be stored for long periods without appreciable decomposition.[15]

Treatment of **1** and **2** (n = 5 or 6) in ethereal solutions at 0° with ethereal diazomethane (0°) led to the immediate discharge of the red coloration of the dithione solutions with no evolution of nitrogen. Removal of the excess diazomethane and ether at 0° under vacuum led to quantitative yields of white solids. On dissolving in ether and cooling to −25° beautiful colorless crystals were obtained. The bis adducts from **1** and **2** (n = 5 or 6) can be formulated as the stereoisomeric bis-Δ^3-1,3,4-thiadiazolines **12** and **13** (n = 5 or 6), respectively. These structural assignments are based on analytical and spectroscopic data.

The infrared spectra of **12** and **13** (n = 5 or 6) exhibited absorptions at 1570 cm^{-1} (–N=N–).[16,17] The nmr absorptions for these thiadiazolines are tabulated in Table I.

TABLE I

NMR ABSORPTIONS FOR THE BIS-Δ^3-1,3,4-THIADIAZOLINES **12** AND **13**

Δ^3-1,3,4-Thiadiazolines[a]	δ, CH_3 or ring CH_2	δ, $SCH_2N{=}N$
12	0.95 (s), 1.25 (s), 1.34 (s)	5.82 (s)[b]
13 (n = 6)	1.25 (broad), 1.85 (broad)	5.82 (s), 5.85 (s)[c,d]
13 (n = 5)	1.45 (complex m), 2.0 (complex m)	5.79 (s), 5.75 (s)[c,e]

[a] $CDCl_3$ as solvent. [b] The cis and trans bis adducts are obtained with the approximate composition being 70% of one isomer and 30% of the other. No definite stereochemical assignments can be presently made. Attempts to separate the isomers have been unsuccessful. [c] The cis and trans bis adducts exhibit different field positions for the δ $SCH_2N{=}N$ resonances. [d] The areas of the δ 5.85 and 5.82 peaks (3:1 ratio) indicate 75% of one isomer and 25% of the other. [e] The peak heights of the δ 5.79 and 5.75 peaks (~1:2 ratio) indicate 67% of one isomer and 33% of the other.

It can be noted from the nmr data presented in Table I that the resonances at δ 5.75–5.85 ppm are only consistent with the formulation of the adducts as bis-Δ^3-1,3,4-thiadiazolines rather than the alternative formulation as Δ^2-1,2,3-thiadiazolines ($SN{=}NCH_2$). Compound **4** exhibits a singlet at δ 5.70 and a discussion is presented for favoring this structural assignment.[11] Indeed the recent unambiguous synthesis and nmr data for **11** (R = R_2 = *tert*-Bu; R_1 = H) and **11** (R = R_2 = Et; R_1 = H) offer support to these assignments. The former compound exhibits absorptions at δ 5.9–6.25 (m) and the latter compounds absorb at δ 5.62 (s), these absorptions being assigned to the protons on the ring carbon adjacent to the sulfur and the –N=N– bond.[14a,b]

The bis-Δ^3-1,3,4-thiadiazolines **12** and **13** (n = 5 or 6) are stable for short periods at room temperature in the solid state. On standing for longer periods (few days) they slowly lose nitrogen. When a 0.5-g sample of **12** was heated in an oil bath, at about 60°, the compound *exploded* and shattered the flask. The compounds can be stored for long periods at −25° without appreciable decomposition. This report along with the previous work of Diebert[11] appears to be the only case in which Δ^3-1,3,4-thiadiazolines have been obtained from the dipolar addition of diazomethane to a thioketone. The bis-Δ^3-1,3,4-thiadiazolines **12** and **13** (n = 5 or 6) are considerably more stable than **4**.[11]

The addition of diazomethane to the dithiones **1** and **2** (n = 5 or 6) leads exclusively to the diadducts in

(12) W. J. Middleton and W. H. Sharkey, *J. Org. Chem.*, **30**, 1384 (1965).

(13) A. Schönberg, B. Konig, and E. Singer, *Chem. Ber.*, **100**, 767 (1967), and references therein cited.

(14) (a) R. M. Kellogg and S. Wassenaar, *Tetrahedron Lett.*, 1987 (1970); (b) R. M. Kellogg, S. Wassenaar, and J. Buter, *ibid.*, 4689 (1970); (c) D. H. R. Barton, E. H. Smith, and B. J. Willis, *Chem. Commun.*, 1226 (1970).

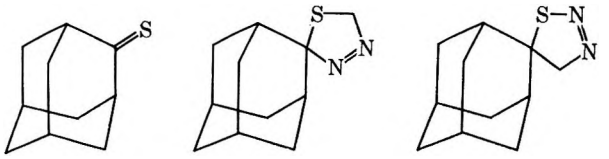
(15) We wish to express our appreciation to Dr. E. U. Elam (Eastman Kodak Co., Kingsport, Tenn.) for generous samples of **1** and **2** (n = 6) for our initial studies (Dec 1969).

(16) Reference 11 reports absorption at 1565 cm^{-1} for compound **4**. References 14a and 14c report absorption for **10** at 1579 and 1575 cm^{-1} (KBr), respectively.

(17) For other reports of systems with –N=N– absorptions in this region, see (a) E. L. Allred and J. C. Hinshaw, *J. Amer. Chem. Soc.*, **90**, 6885 (1968); (b) R. J. Crawford, A. Mishra, and R. J. Dummel, *ibid.*, **88**, 3959 (1966).

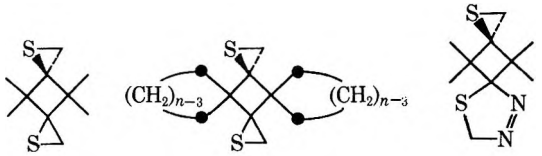
which the nitrogen end of the diazomethane has bonded to the carbon of the thione link. The intimate details of the cycloaddition mechanism are left unanswered. However, because of the steric barrier of the bulky groups surrounding the C=S bonds in **1** and **2** (n = 5 or 6), it is possible that approach of the nitrogen end of the diazomethane to the carbon of the thione link is sterically more favorable in comparison to the approach of the carbon end (with the two hydrogens) to the carbon of the thione link. It is perhaps of interest to report some preliminary data on the cycloaddition of diazomethane with adamantanethione (**14**),[7] a molecule in which the thione grouping is not so sterically inaccessible as in the cases of the dithiones reported above.

Treatment of **14** with ethereal diazomethane (0°) led to the immediate discharge of the orange coloration of the solution. Concentration of the solution at 0° led to an oil which solidified in the freezer (−25°). Nmr examination of the crude product ($CDCl_3$) revealed absorptions at δ 1.9 (broad d), 2.7 (two broad peaks), 5.0 (s), and 5.82 ppm (s). The peak at δ 5.82 can be assigned to the protons of the Δ^3-1,3,4-thiadiazoline ring in **15** and the δ 5.0 peak to the protons of the Δ^2-1,2,3-thiadiazoline ring in **16**, the percentages of **15** and **16** in the reaction mixture being 75 and 25%, respectively (area integration of the singlets). The infrared spectrum of the mixture (neat) exhibited -N=N- stretching frequencies at 1575 (**15**) and 1515 cm^{-1} (**16**) of about equal intensities. Thus in the case of adamantanethione cycloaddition occurs *via* the two possible modes. This reaction is under further investigation.



14 **15** **16**

Diepisulfide Formation. Thermal Decompositions of the Bis-Δ^3-1,3,4-thiadiazolines.—The bis-Δ^3-1,3,4-thiadiazolines **12** and **13** (n = 5 or 6) on refluxing in chloroform or carbon tetrachloride–hexane solutions (2–3 hr) readily lost nitrogen and were quantitatively converted into stereoisomeric mixtures of the diepisulfides **17** and **18** (n = 5 or 6), respectively. The nmr data for these diepisulfides are tabulated in Table II.



17 **18** **19**

On repeated crystallization of the crude diepisulfide mixture **17** from pentane–benzene the pure trans diepisulfide **17** could be isolated. It exhibited resonances in the nmr at δ 2.59 (s, SCH_2, 4 H) and 1.05 ppm (s, CH_3, 12 H). The decomposition of the bis-Δ^3-1,3,4-thiadiazoline **12** leads to 70% *trans*-**17** and 30% *cis*-**17** [CH_3 resonances at 1.26 (s) and 0.90 (s)].

When a solution of **12** ($CDCl_3$) was allowed to stand at room temperature for 24 hr, the nmr pattern became complex as about nine distinct CH_3 singlets appeared in the δ 0.8–1.5 ppm region and singlets appeared at δ 2.55 and 2.59 ppm. The singlet originally present at δ 5.82 ppm diminished in intensity and a new singlet appeared at δ 5.75. The new absorptions δ 2.55 and 5.75 (not present in the product diepisulfides **17** or the starting thiadiazolines **12**) are consistent with the formation of the Δ^3-1,3,4-thiadiazoline intermediate **19** as a transient in the decomposition pathway to **17**.

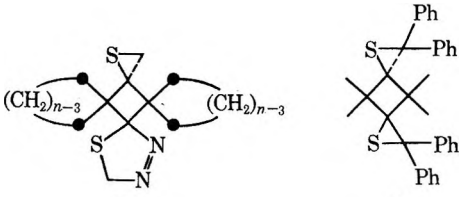
TABLE II

NMR SPECTRAL DATA FOR THE STEREOISOMERIC DIEPISULFIDES **17** AND **18**

Diepisulfides[a]	δ, CH_3 or ring CH_2	δ, CH_2S[b]
17	0.90 (s), 1.05 (s), 1.26 (s)	2.59 (s)
18 (n = 6)	1.26 (broad m), 1.57 (broad m)	2.68 (s), 2.61 (s)
18 (n = 5)	1.40 (complex m), 1.80 (complex m)	2.62 (s), 2.55 (s)

[a] $CDCl_3$ as solvent. Area integrations are in agreement with the structural assignments. [b] Reference 11 reports δ 2.55 (s) for the corresponding protons in **19**. Reference 10 lists several episulfides with resonances at δ 2.1–2.4 ppm.

On the basis of the areas of the protons of the episulfide rings, the stereoisomeric composition of the diepisulfides **18** (n = 5) was 67% of one isomer and 33% of the other (no definite stereochemical assignment could be made). The thermal decomposition of **13** (n = 5) was monitored in the nmr tube (CCl_4). After 2 hr singlets appeared at δ 2.37 and 2.85 ppm [probably SCH_2 of the stereoisomeric Δ^3-1,3,4-thiadiazolines **20** (n = 5)] and δ 2.50 and 2.57 [SCH_2 of the diepisulfides **18**, n = 5)]. In addition the singlet at δ 5.75 diminished in intensity. After 8 hr the signals at δ 2.37, 2.85, 2.57, and 2.50 ppm increased in intensity and the singlet at δ 5.75 decreased. After warming the tube, the singlets δ 2.50 and 2.57 remained.



20 **21**

On the basis of the singlets at δ 2.62 and 2.55 (SCH_2) the diepisulfide composition for **18** (n = 6) was about 70% of one isomer and 30% of the other isomer. The decomposition of bis adduct **13** (n = 6) was monitored in the nmr tube (CCl_4). After 3 hr a new singlet appeared at δ 5.80 ppm (in addition to the singlets at δ 5.75 and 5.78 ppm) and additional singlets appeared at δ 2.74 and 2.44 (equal intensity) and δ 2.64 and 2.56 (different intensity, SCH_2). After about 4 hr at room temperature the intensity of the δ 2.64 and 2.56 peaks increased and the δ 5.75 peak of the original bis-Δ^3-1,3,4-thiadiazoline decreased as the δ 5.80 peak increased in intensity. After 7 hr the diepisulfide peaks intensified (δ 2.64 and 2.55) and the peaks at δ 2.74 and 2.44 diminished in intensity. The nmr data are consistent with the buildup of the stereoisomeric Δ^3-1,3,4-thiadiazoline **20** (n = 6), followed by a slower decomposition to the diepisulfides.

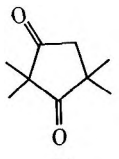
The bis-Δ^3-1,3,4-thiadiazoline **13** (n = 5) (nmr studies) is the most stable and undergoes the slowest de-

composition, and the bis adduct **12** undergoes the fastest decomposition. This is perhaps suggestive of a release of steric compression in the decomposition of **12** in comparison to **13** ($n = 5$). Kellogg has previously discussed the mechanism of thermolysis of several Δ^3-1,3,4-thiadiazolines as proceeding *via* thiocarbonyl ylides.[14]

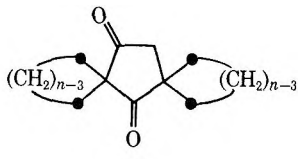
The thermal decomposition of the adducts obtained from **14** was also monitored in the nmr tube ($CDCl_3$). After about 0.5 hr at 60° the absorption at δ 5.82 disappeared but the peak at δ 5.0 remained. A new peak appeared at δ 2.4 (episulfide protons). At 85° for 3 hr the δ 5.0 peak disappeared but the nmr pattern in the δ 1.7–2.3 region was drastically changed and indicated decomposition of the episulfide. Apparently **15** (*via* a thiocarbonyl ylide[14]) undergoes loss of nitrogen more readily than **20**. These points are under further investigation.

Diphenyldiazomethane Reaction with 1.—The addition of an ethereal solution of diphenyldiazomethane to an ether solution of dithione **1** led to the immediate evolution of nitrogen. After 1 hr the nitrogen evolution ceased and on evaporation of the ether a quantitative yield of the stereoisomeric diepisulfides **21** was obtained. The nmr ($CDCl_3$) showed resonances at δ 7.80 (aromatic complex m), 7.2 (aromatic complex m), 1.42 (s), 0.77 (s), and 0.53 ppm (s). Treatment of the crude diepisulfide mixture with warm acetone left an insoluble white residue which exhibited resonances at δ 7.8 (aromatic complex m), 7.2 (aromatic complex m), and 0.77 ppm (s) and can be assigned the transoid structure **21**. The acetone-soluble portion on cooling led to the cis diepisulfide **21** which exhibited nmr peaks at ($CDCl_3$) δ 7.8 (aromatic complex m), 7.2 (aromatic complex m), 1.42 (s), and 0.53 ppm (s). The original diepisulfide mixture consisted of 67% *cis*-**21** and 33% *trans*-**21**.

Dione–Diazomethane Ring Expansions.—Treatment of the diones **1** (S = O) and **2** ($n = 4$, 5, or 6; S = O) with an ethereal–ethanolic solution of diazomethane led to the ring-expanded diones **22** and **23** ($n = 4$, 5, or



22



23

6), respectively. The dione **22** was obtained quantitatively by allowing the reaction mixture to stand at room temperature for about 3 days. Shorter reaction periods led to incomplete reaction. The dione **22** exhibited resonances in the nmr at (CCl_4) δ 1.10 (s), 1.21 (s), and 2.55 ppm (s). The nmr data for the diones **23** ($n = 4$, 5, or 6) are tabulated in Table III.

TABLE III

NMR SPECTRAL DATA FOR THE DIONES **23** ($n = 4$, 5, OR 6)

Dione 23[a]	δ, $CH_2C{=}O$	δ, ring CH_2
4	2.84 (s)	1.8–2.6 (complex m)
5	2.70 (s)	1.84 (broad peak)
6	2.63 (s)	1.60 (broad peak)

[a] $CDCl_3$ as solvent.

The slowest ring expansion occurred with dione **2** ($n = 6$; S = O). After 2 days at room temperature with excess diazomethane only a 30% yield of pure **23** ($n = 6$) could be obtained. The dione **2** ($n = 4$; S = O) reacted instantaneously on addition of the diazomethane solution. Nitrogen was evolved and a quantitative yield of **23** ($n = 4$) could be obtained. The order of reactivity with ethanolic–ethereal diazomethane is dione **2** ($n = 4$; S = O) >>>> dione **2** ($n = 5$; S = O) >> dione **1** (S = O) > dione **2** ($n = 6$; S = O). No epoxide products were detectable. The mechanism of diazoalkane ring expansions have been discussed in several reviews and papers.[18]

One can perhaps explain the rapid rate of ring expansion of **2** ($n = 4$; S = O) on the basis of a synchronous addition–rearrangement mechanism.[18d] The internal angle strain of the cyclobutane ring holding the carbonyl groups could be considerable because of the external angles (about 90°) of the spirocyclobutane rings. Release of this internal angle strain would be expected to lead to a facile ring expansion process. In so far as release of internal angle strain, the order of reactivity for the spiro systems would be **2** ($n = 4$; S = O) >> **2** ($n = 5$; S = O) > **2** ($n = 6$; S = O). One must also consider the steric accessibility of the carbonyl group. The dione **1** (S = O) would probably be the most sterically crowded around the carbonyl group for approach of the diazomethane molecule while the dione **2** ($n = 4$; S = O) would be least hindered by the adjacent spiro methylene groups. Thus utilizing angle strain and steric accessibility arguments, the order of the reactivity of the diones can be adequately rationalized. The question of whether a discrete intermediate is involved in the ring expansion processes is unanswered.

Experimental Section

Melting points are uncorrected; elemental analyses were performed by Robertson Laboratory, Florham Park, N. J. 07932. Nmr spectra were recorded on a Varian Associates Model A-60 spectrometer using tetramethylsilane as an internal standard. Infrared spectra were recorded on a Perkin-Elmer Model 21 spectrometer or a PE 237B spectrometer.

Materials.—Diazomethane was generated from Diazald (*N*-methyl-*N*-nitroso-*p*-toluenesulfonamide, Aldrich Chemical Co.).[19]

Dithione Syntheses. A. 2,2,4,4-Tetramethyl-1,3-cyclobutanedithione (1).—The procedure was adapted from the Lipscomb patent and is documented here for reference.[4b] A solution of 2,2,4,4-tetramethyl-1,3-cyclobutanedione (25.0 g, 0.18 mol) and freshly fused zinc chloride (12.5 g, 0.092 mol) in methanol (200 ml) was placed in a 500-ml three-necked round-bottom flask equipped with a gas inlet tube, a gas outlet tube, and a thermometer. The solution was cooled to −5° and hydrogen chloride gas was bubbled through the reaction mixture for 1 hr. During this period the temperature of the solution rose and then dropped back to −5°. Hydrogen sulfide was then bubbled through the mixture for 14 hr at 0°. The red crystalline product which separated was filtered and washed with cold methanol (10–15 ml), wt 20 g. The crude dithione was crystallized from methanol (50 ml) to yield 16.0 g (52%) of pure dithione **1** as red platelets, mp 124–125° (lit.[4b] mp 125–126°). The dithione **1** could also be readily purified by sublimation.

(18) (a) C. D. Gutsche, *Org. React.*, **8**, 364 (1954); (b) C. D. Gutsche and D. Redmore, "Carbocyclic Ring Expansion Reactions," Academic Press, New York, N. Y., 1968; (c) J. A. Marshall and J. J. Partridge, *J. Org. Chem.*, **33**, 4090 (1968); (d) N. J. Turro and R. B. Gagosian, *J. Amer. Chem. Soc.*, **92**, 2036 (1970); (e) G. W. Cowell and A. Ledwith, *Quart. Rev., Chem. Soc.*, **24**, 119 (1970), for a review and mechanistic discussion.

(19) (a) H. B. Hopps, *Aldrichimica Acta*, **3**, 9 (1970); (b) T. J. de Boer and H. J. Backer, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 250.

The nmr (CCl_4) exhibited a singlet at 1.40 ppm (lit.[4a] 1.40 ppm).

B. Dispiro[4.1.4.1]dodecane-6,12-dithione (2, n = 5).—Following the procedure described above, dispiro[4.1.4.1]dodecane-6,12-dione[20] (5.0 g, 0.026 mol) was converted into 4.5 g (78%) of crude dithione **2** (n = 5). The product was crystallized from cold methanol to yield orange-red platelets which melted at room temperature (22°), nmr (CCl_4) δ 1.95 ppm (m).

Anal. Calcd for $C_{12}H_{16}S_2$: C, 64.27; H, 7.19; S, 28.54. Found: C, 63.95; H, 7.50; S, 28.30.

C. Dispiro[5.1.5.1]tetradecane-7,14-dithione (2, n = 6).—Following the procedure described above with the exception that ethanol (150 ml) and methanol (50 ml) was used as the solvent, dispiro[5.1.5.1]tetradecane-7,14-dione[20] (10 g, 0.046 mol) yielded 10.0 g (86%) of crude dithione **2** (n = 6). The dithione was recrystallized from methanol, mp 119–120°, nmr (CCl_4) δ 1.77 ppm (broad peak).

Anal. Calcd for $C_{14}H_{20}S_2$: C, 66.64; H, 7.99; S, 25.37. Found: C, 66.50; H, 8.00; S, 25.32.

Diazomethane Additions to the Dithiones. General Procedure.—A slight excess of alcohol-free ethereal diazomethane at 0° was added to an ethereal solution of the dithione at 0°. Nitrogen evolution did not occur and the addition was continued until the red color disappeared and the yellow color persisted. The ether and excess diazomethane were removed at 0° using a slow nitrogen stream and then the last traces of ether were removed under vacuum. The white solids were stable at 0° and could readily be recrystallized from ether at low temperature.

A. Bis-Δ³-1,3,4-thiadiazolines 12.—Treatment of **1** (3.4 g, 0.02 mol) with excess diazomethane led to a quantitative yield of crude **12**. The compound was recrystallized from ether at −25°, mp 58° (decomposition starts), white solid fills tube, 180–195° to clear melt. The following spectral data were obtained for **12**: ir (CCl_4) 1570 cm^{-1} (N=N); nmr ($CDCl_3$) δ 0.95, 1.25, 1.34 (all singlets, combined area for 12 H, CH_3), and 5.82 ppm (singlet, 4 H, SCH_2N=N).

Anal. Calcd for $C_{10}H_{16}N_4S_2$: C, 46.87; H, 6.29; N, 21.87. Found: C, 46.88; H, 6.03; N, 21.70.

B. Bis-Δ³-1,3,4-thiadiazoline 13 (n = 5).—Treatment of **2** (n = 5) with excess diazomethane led to a quantitative yield of the stereoisomers **13**: ir (CCl_4) 1570 cm^{-1} (N=N); nmr ($CDCl_3$) δ 5.79, 5.75 (both singlets, combined area for 4 H, SCH_2N=N), 1.45 and 2.0 ppm (complex multiplets, combined area for 16 H, ring CH_2).

Anal. Calcd for $C_{14}H_{20}N_4S_2$: C, 54.53; H, 6.54; N, 18.17. Found: C, 54.55; H, 6.29; N, 18.07.

C. Bis-Δ³-1,3,4-Thiadiazolines 13 (n = 6).—Treatment of **2** (n = 6) with excess diazomethane led to a quantitative crude yield of the stereoisomers **13** (n = 6): ir (CCl_4) 1570 cm^{-1} (N=N); nmr ($CDCl_3$) δ 5.85, 5.82 (both singlets, combined area for 4 H, SCH_2N=N), 1.85 and 1.25 ppm (broad patterns, combined area for 20 H, ring CH_2).

Anal. Calcd for $C_{16}H_{24}N_4S_2$: C, 57.13; H, 7.19; N, 16.66. Found: C, 57.41; H, 7.25; N, 16.79.

Thermolyses of the Stereoisomeric Bis-Δ³-1,3,4-thiadiazolines.—The bis adducts were refluxed in chloroform or carbon tetrachloride–hexane solutions for 2–4 hr (until the evolution of nitrogen ceased). On evaporation of the solvent the crude diepisulfides could be obtained.

A. Diepisulfides 17.—The bis adducts **12** (1.3 g) on refluxing in chloroform (10 ml) for 4 hr yielded 1.0 g (96%) of the stereoisomeric mixture of diepisulfides **17**, mp 150–185°. The crude product showed nmr absorptions at ($CDCl_3$) δ 0.90, 1.05, 1.26 (all singlets, combined total area for 12 H, CH_3), and 2.59 ppm (singlet, 4 H, SCH_2). On crystallization from pentane the intensities of the singlets at δ 0.90 and 1.26 diminished and the melting point was raised to 195–199°. Several recrystallizations from benzene–pentane yielded the pure trans diepisulfide: mp 207–208°; nmr ($CDCl_3$) δ 1.05 (s, 12 H, CH_3) and 2.59 ppm (s, 4 H, SCH_2).

Anal. (once crystallized from pentane). Calcd for $C_{10}H_{16}S_2$: C, 59.98; H, 8.05; S, 31.92. Found: C, 60.22; H, 8.09; S, 31.70.

B. Diepisulfides 18 (n = 5).—The bis adducts **13** (n = 5) were refluxed in a carbon tetrachloride–hexane solution until the evolution of nitrogen ceased. A quantitative yield of the diepisulfides **18** (n = 5) was obtained. The following nmr data were obtained ($CDCl_3$): δ 1.40, 1.80 (broad complex m, combined area for 16 H, ring CH_2), 2.62 and 2.55 ppm (both singlets, combined area for 4 H, SCH_2).

The analytical sample was crystallized from pentane, mp 65–71°.

Anal. Calcd for $C_{14}H_{20}S_2$: C, 66.64; H, 7.98; S, 25.37. Found: C, 66.74; H, 8.01; S, 25.58.

C. Diepisulfides 18 (n = 6).—The bis adducts **13** (n = 6) (0.9 g) in chloroform (10 ml) were refluxed for 1 hr. On evaporation of the chloroform a quantitative yield of the diepisulfides **18** (n = 6) was obtained, mp 87–97°. On crystallization from pentane the mixture melted at 99–102° (little change in the nmr spectrum).

The following nmr data were recorded ($CDCl_3$): δ 1.26, 1.57 (broad m, combined area for 20 H, ring CH_2), 2.61 and 2.68 ppm (both singlets, combined area for 4 H, SCH_2).

Anal. Calcd for $C_{16}H_{24}S_2$: C, 68.54; H, 8.63; S, 22.83. Found: C, 68.69; H, 8.25; S, 23.03.

Isolation of *cis*- and *trans*-21. Addition of Diphenyldiazomethane to 1.—To a solution of 2,2,4,4-tetramethyl-1,3-cyclobutanedithione (0.4 g, 0.0023 mol) in ether a solution of diphenyldiazomethane (1.2 g, 0.006 mol) in ether was added slowly at room temperature. The reaction mixture was allowed to stand until the evolution of nitrogen ceased (1 hr). The solid which separated was filtered and washed with cold pentane. The filtrate was concentrated and pentane was added to the residue. The red solution was decanted from the white crystalline solid: total wt 1.15 g (quantitative); mp 235–240°; nmr ($CDCl_3$) δ 7.80 (aromatic complex m), 7.2 (aromatic complex m), 1.42, 0.77, and 0.53 ppm (all singlets, SCH_2). The product was recrystallized from benzene–hexane and the isomer composition changed.

Anal. Calcd for $C_{34}H_{32}S_2$: C, 80.90; H, 6.39; S, 12.71. Found: C, 81.02; H, 6.56; S, 12.99.

Treatment of the isomeric mixture (cis:trans 67:33) with warm acetone left an insoluble white residue, mp 256–257° The nmr ($CDCl_3$) showed peaks at δ 7.8 (broad multiplet), 7.25 (broad m), and 0.79 ppm (s), which is the *trans*-**21**. The acetone washings were combined and the solvent was removed. The residual solid was taken up in cold acetone and filtered from the insoluble material. The filtrate was partially concentrated and cooled to yield *cis*-**21**: mp 252–253°; nmr δ ($CDCl_3$) 7.8 (broad m), 7.2 (broad m), 1.43 (s), and 0.53 ppm (s).

Diazomethane Ring Expansions. Preparation of 22.—Treatment of tetramethyl-1,3-cyclobutanedione (2.8 g, 0.02 mol) with excess ethanolic–ethereal diazomethane (−25° for 21 hr and room temperature for 3 days) followed by removal of the ether left a low-melting solid in quantitative yield. Crystallization from pentane yielded 2.97 g (96%) of pure product: mp 22–23°; ir (neat) 1725 (s), 1760 and 1695 cm^{-1} (sh); nmr (CCl_4) δ 1.10 (s, 6 H, CH_3), 1.21 (s, 6 H, CH_3), and 2.55 ppm (s, 2 H, CH_2-C=O).

Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 70.10; H, 9.26.

Preparation of 23 (n = 4).—Treatment of dione **2** (n = 4; S = O) (0.14 g, 0.85 mol) in ether with excess ethanolic–ethereal diazomethane led to the instantaneous evolution of nitrogen. The solution was cooled to −25° and the solid which separated was collected, wt 0.052 g, mp 50–52°. On removal of the ether a second crop was obtained (total yield 99%) of the same melting point. The analytical sample was prepared by sublimation: mp 51–52.5°; ir ($CHCl_3$) 1712 (s) and 1752 cm^{-1} (shoulder); nmr ($CDCl_3$) δ 1.8–2.6 (complex m, 12 H, ring CH_2) and 2.84 (s, 2 H, CH_2C=O).

Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 73.83; H, 8.18.

Preparation of 23 (n = 5).—Excess ethanolic–ethereal diazomethane was added to **2** (n = 5) (2.0 g, 0.011 mol) in ether. The solution was kept at −25° for 18 hr, 8 hr at 0°, and at room temperature for 24 hr. On removal of the excess diazomethane and ether an oil was obtained in a quantitative yield. This product was essentially pure and could be crystallized at low temperature from pentane and melted slightly below room temperature: ir (neat) 1710 (s), 1750 cm^{-1} (sh); nmr ($CDCl_3$) δ 1.84 (broad peak, 16 H, ring CH_2) and 2.70 ppm (s, 2 H, CH_2C=O).

Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.65; H, 9.03.

Preparation of 23 (n = 6).—Dione **2** (n = 6) (4.0 g, 0.018 mol) was treated with excess ethanolic–ethereal diazomethane and kept at −25° for 18 hr, 0° for 8 hr, and at room temperature for 2

(20) J. L. E. Erickson, F. E. Collins, Jr., and B. L. Owen, *J. Org. Chem.*, **31**, 480 (1966).

days. On removal of the excess diazomethane and ether, a large amount of starting material was present. By repeated crystallization from pentane the starting material could be removed and 1.3 g (31%) of crude dione **23** (n = 6) was obtained, mp 63–69°. The analytical sample was prepared by sublimation, mp 74–75°. The dione **23** (n = 6) had the following spectral properties: ir ($CHCl_3$) 1725 (s), 1725 and 1784 cm^{-1} (sh); nmr ($CDCl_3$) δ 1.6 (broad absorption, 20 H, ring CH_2), and 2.63 ppm (s, 2 H, $CH_2C{=}O$).

Anal. Calcd for $C_{15}H_{20}O_2$: C, 76.88; H, 9.46. Found: C, 76.75; H, 9.70.

Registry No.—**2** (n = 5), 31934-25-5; **2** (n = 6), 22502-49-4; *cis*-**12**, 31934-27-7; *trans*-**12**, 31934-28-8; *cis*-**13** (n = 5), 31934-29-9; *trans*-**13** (n = 5), 31934-30-2; *cis*-**13** (n = 6), 31934-31-3; *trans*-**13** (n = 6), 31934-32-4; **15**, 31934-33-5; **16**, 31934-34-6; *cis*-**17**, 31934-35-7; *trans*-**17**, 31934-36-8; *cis*-**18** (n = 5), 31981-32-5; *trans*-**18** (n = 5), 31934-37-9; *cis*-**18** (n = 6), 31934-38-0; *trans*-**18** (n = 6), 31934-39-1; *cis*-**21**, 31934-40-4; *trans*-**21**, 31934-41-5; **22**, 31934-42-6; **23** (n = 4), 31934-43-7; **23** (n = 5), 31934-44-8; **23** (n = 6), 31934-45-9; diazomethane, 334-88-3.

Acknowledgment.—Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research (PRF 3437-A1, 4).

6-Acyl-5*H*-1-pyrindine-5,7(6*H*)-diones and Their Reaction with Hydrazine

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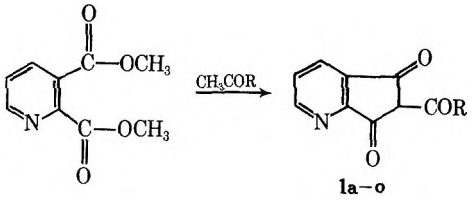
Received February 26, 1971

A series of 6-acyl-5*H*-1-pyrindine-5,7(6*H*)-diones (**1**) was prepared by condensing dimethyl 2,3-pyridinedicarboxylate with various methyl ketones. Depending upon the conditions, reaction of compounds **1** with hydrazine gave 3-substituted 1,4-dihydropyrazolo[3′,4′:3,4]cyclopenta[1,2-*b*]pyridines (**6**), 3-substituted pyrazolo[3′,4′:3,4]cyclopenta[1,2-*b*]pyridin-4(1*H*)-ones (**2**), or a mixture of the hydrazones of the two isomeric 3-substituted pyrazolo[3′,4′:3,4]cyclopentapyridin-4(1*H*)-ones (**4** and **5**).

Our interest in 2-acyl-1,3-indandiones and their reaction products with hydrazine[1-3] prompted us to prepare the structurally related compounds, the 6-acyl-5*H*-1-pyrindine-5,7(6*H*)-diones (**1a–o**) and to study their reaction with hydrazine. 6-Alkyl- and 6-aryl-5*H*-1-pyrindine-5,7(6*H*)-diones are reported in the literature[4,5] but no reference was found concerning the 6-acyl derivatives **1**.

The structural analogy with the 6-acyl-1,3-indandiones suggested the preparation of **1** by a method similar to that used to prepare the acylindandiones.[1] Yields varying from 8 to 69% were obtained by reacting dimethyl 2,3-pyridinedicarboxylate with the appropriate methyl ketone in the presence of sodium methoxide.

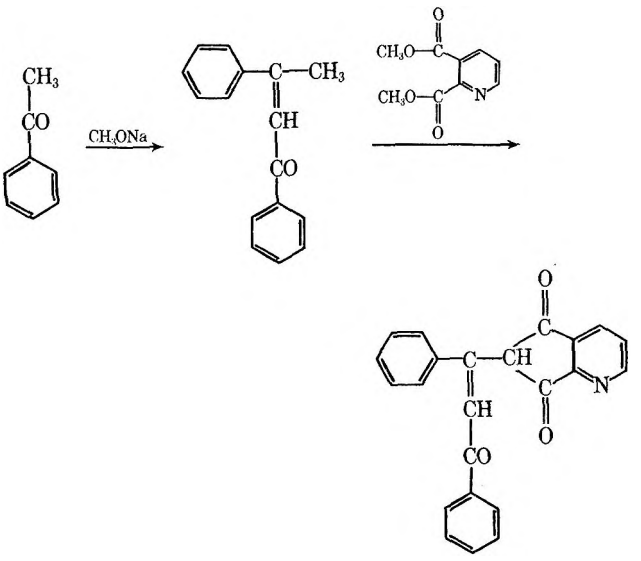


1a–o

When R is an aryl group instead of an alkyl, the reaction is slower and it is accompanied by side reactions. Thus, in the condensation of dimethyl 2,3-pyridinedicarboxylate with acetophenone to form compound **1m**, 6-(α-phenacylidenebenzyl)-5*H*-1-pyridine-5,7(6*H*)-dione was isolated as the by-product.

The structures of the acylpyrindinediones **1a–o** are based upon the elemental analyses and are consistent with the infrared spectra.

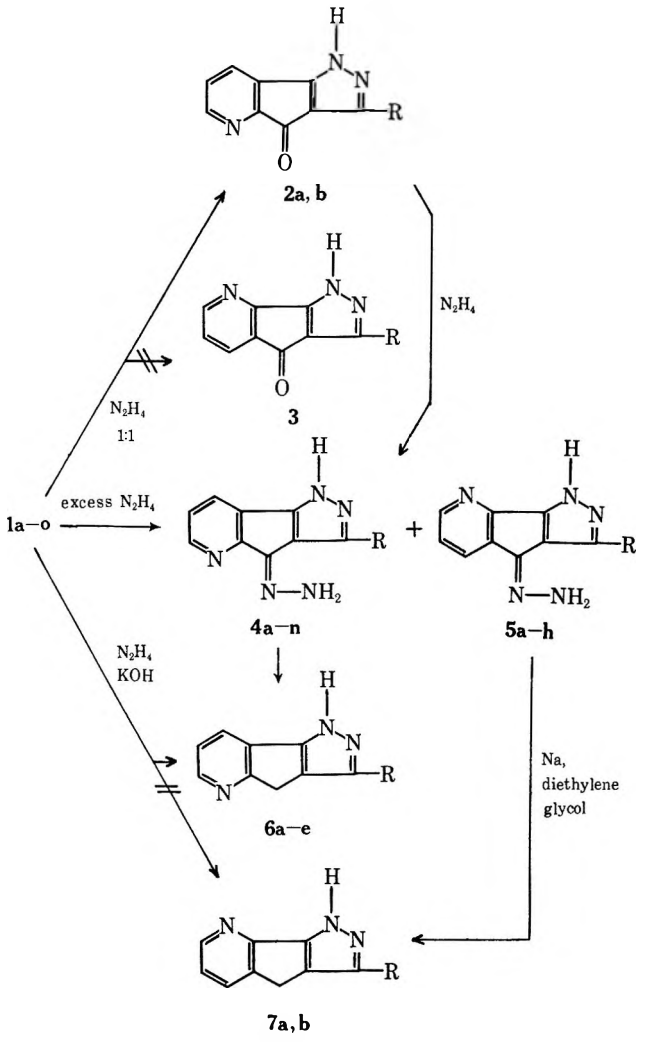
The addition of hydrazine to a hot solution of 6-acetyl-5*H*-1-pyrindine-5,7(6*H*)-dione (**1a**) in ethanol, followed by rapid cooling in ice, gave the corresponding monohydrazone with the hydrazono group on the side chain. This structural assignment was based on the similarities of the spectral and chemical properties of this hydrazone with those of the known α-hydrazone of 2-acetyl-1,3-indandione.[1] Several attempts to prepare the monohydrazones of other 6-acyl-5*H*-1-pyrindine-5,7(6*H*)-diones were unsuccessful. The products obtained were generally the ring-closed compounds **2**.



In the reaction of the acylpyrindinediones **1m** and **1n** with 1 equiv of hydrazine in refluxing ethanol, only one of the two possible isomers, 3-substituted pyrazolo[3′,4′:3,4]cyclopenta[1,2-*b*]pyridin-4(1*H*)-one (**2**, Scheme I) or 3-substituted pyrazolo[3′,4′:3,4]-cyclopenta[2,1-*b*]pyridin-4(1*H*)-one (**3**), was isolated. Structure **2** was assigned to the isolated isomer, since the hydrazones of compounds **2** were found identical

(1) R. A. Braun and W. A. Mosher, *J. Amer. Chem. Soc.*, **80**, 2749 (1958).
(2) R. A. Braun and W. A. Mosher, *J. Org. Chem.*, **24**, 648 (1959).
(3) W. A. Mosher and W. E. Meier, *ibid.*, **35**, 3685 (1970).
(4) B. M. Bain and J. E. Saxton, *J. Chem. Soc.*, 5216 (1961).
(5) L. E. Neiland and G. Ya. Vanag, *Khim. Geterotsikl. Soedin.*, **1**, 114 (1967); *Chem. Abstr.*, **67**, 64269*k* (1967).

SCHEME I[a]



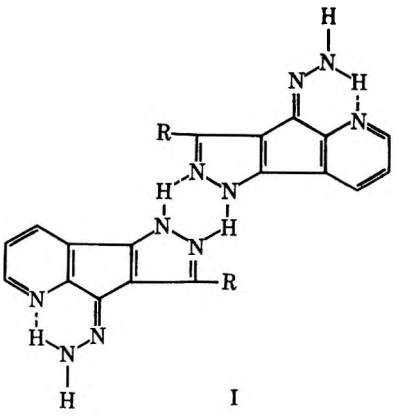
[a] For R see Tables I–III and Experimental Section.

with the hydrazones **4** prepared directly from compounds **1** as described below.

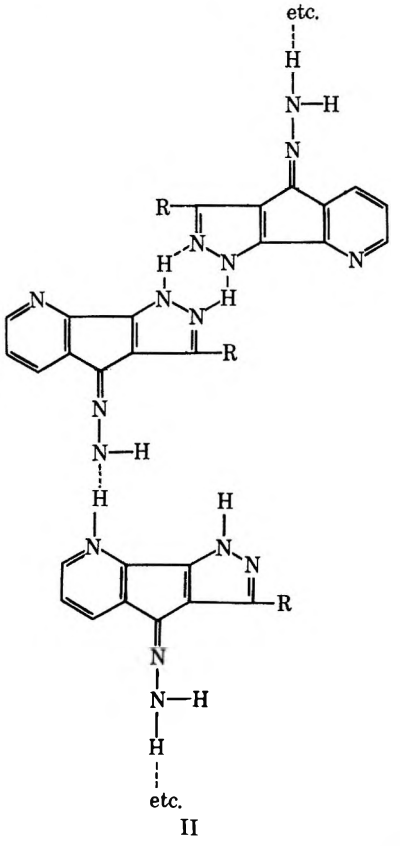
Considering the similarity of this reaction with that between 2-acetyl-4-nitro-1,3-indandione and hydrazine, in which 3-methyl-8-nitroindeno[1,2-*c*]pyrazol-4(1*H*)-one was obtained,[3] one would predict that isomer **3** would be formed preferentially. However, none of this isomer was found. The structure of the tautomer 3-substituted pyrazolo[3′,4′:3,4]cyclopenta-[1,2-*b*]-pyridin-4(2*H*)-one was also considered. The similarity of the infrared spectra of compounds **2** with those of the known 3-substituted indeno[1,2-*c*]-pyrazol-4(1*H*)-ones[2] favors structure **2** and we will use this structure in subsequent discussion without excluding the possibility of the tautomeric structure.

The reaction of the acylpyrindinediones **1** with a large excess of hydrazine in refluxing ethanol yielded in most cases a mixture of two isomeric hydrazones. These compounds were easily separated by means of their different solubilities in benzene. The soluble isomer constitutes the main fraction and shows a lower melting point than the insoluble isomer. When only one isomer was found, it was the benzene-soluble one.

The infrared spectra and the physical properties of these two isomers suggest structure **4** for the benzene-soluble isomer and structure **5** for the benzene-insoluble isomer. Several types of intra- and intermolecular hydrogen bonds are possible in these isomers. Some are shown in structures I and II.



I



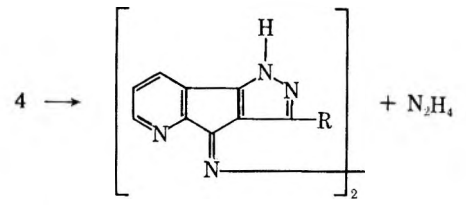
II

The infrared spectra of the benzene-soluble compounds show a broad and weak band at 3360 cm^{-1}, which is tentatively assigned to an intramolecular hydrogen-bonded NH_2 group, and very broad and weak bands at 3150 and 3050 cm^{-1}, which may be assigned to an intermolecular hydrogen-bonded NH group, as represented in I. This structure also shows the type of intermolecular hydrogen bonding which can lead to a dimer, and this accounts for the relatively low melting points of the isomers **4** in comparison with isomers **5** and for their solubility in nonpolar solvents.

The infrared spectra of the benzene-insoluble compounds show a sharp band at 3350 cm^{-1}, which is tentatively assigned to free NH_2 groups (from terminal hydrazono group), and bands at 3220 and 3160 cm^{-1}, which may be assigned to associated NH_2 and NH groups, respectively. These associated bands are not quite so broad as those shown by the benzene-soluble compounds. Structure II shows the type of intermolecular hydrogen bonding which can lead to

polymers, and this accounts for the higher melting points of isomers **5** and for their very low solubilities in nonpolar solvents.

Hydrazones **4** decomposed when heated at about 250° to give the corresponding azines and hydrazine. This



disproportionation reaction can proceed at a lower temperature in the presence of hydrochloric acid. An alternate route to these azines is based on the reaction of the pyrindinediones **1** with excess hydrazine in acetic acid.

The Wolff–Kishner reduction of hydrazones **4** by the Huang–Minlon modification gave the corresponding 3-substituted 1,4-dihydropyrazolo[3′,4′:3,4]-cyclopenta[1,2-*b*]pyridines (**6a–e**). These compounds were also obtained directly from the acylpyrindinediones **1** by using the Wolff–Kishner reduction. In the latter reaction the other possible isomer, the 3-substituted 1,4-dihydropyrazolo[3′,4′:3,4]-cyclopenta-[2,1-*b*]pyridine (**7**), was not found. Compounds **7** instead were obtained when the hydrazones **5** were heated at 210° with sodium in diethylene glycol.

The nmr spectra of compounds **6** and **7** show that the methylene group in **6** is slightly more deshielded than in **7**, indicating the proximity of the nitrogen atom to the methylene group in the former compounds. These results give further evidence for the structures assigned to compounds **4** and **5** from which **6** and **7**, respectively, are derived.

Experimental Section[6]

6-Acyl-5*H*-1-pyridine-5,7(6*H*)-diones (1a–o).—The following general procedure was used. A mixture of dimethyl 2,3-pyridinedicarboxylate (0.0256 mol) and the appropriate methyl ketone (0.0259 mol) in dry benzene (80 ml) was added to a stirred suspension of sodium methoxide (0.13 mol) in dry benzene (100 ml). The mixture was stirred at 40° for 6 hr, then at reflux for 3–4 days. A yellow to brown solid mass adhered to the walls of the flask. The reaction mass was cooled to room temperature and the solvent was decanted into a separatory funnel and washed twice with water. The aqueous washings were added to the solid residue in the reaction flask, boiled with Darco, and filtered hot; the filtrate was cooled in ice. The precipitate was collected by filtration, dissolved in water (50 ml), and acidified with 50% hydrochloric acid. The yellow solid was collected, dried, and recrystallized from petroleum ether (bp 75–90°), unless otherwise indicated (Table I).

The sodium salts of some acylpyrindinediones are very soluble in water and do not crystallize out on cooling. In these cases the alkaline solution, after boiling with Darco, was filtered, cooled, and acidified with 50% hydrochloric acid and the acylpyrindinedione was separated by extraction with ether.

The sodium salt of **1k** is almost insoluble in water. In this case, after the benzene layer was separated, water was added to the solid reaction mass and the mixture was heated on a steam bath. The yellow sodium salt was collected by filtration, washed with water, and suspended in water, and the slurry was made acid to litmus by adding 50% hydrochloric acid under strong agitation. After 3 hr of stirring the solid was collected and crystallized from petroleum ether.

6-Benzoyl-5*H*-1-pyrindine-5,7(6*H*)-dione (1m) was prepared as in the general procedure described above, except that, after the reaction mixture was refluxed for 4 days, 0.5 *N* sodium hydroxide solution (150 ml) was added at room temperature and the benzene layer was separated. The alkaline solution was washed once with ether, boiled with Darco, filtered, acidified with 50% hydrochloric acid, and cooled in ice overnight to give **1m**, as green-yellow crystals.

In another experiment for preparing **1m**, after separation of the benzene layer, the alkaline solution was acidified to pH 5 with 50% hydrochloric acid and the resulting deep red solution was extracted with ether. Removal of the ether and crystallization of the residue from ethanol gave 1.0 g of the by-product, 6-(α-phenacylidenebenzyl)-5*H*-1-pyrindine-5,7(6*H*)-dione as dark violet crystals: mp 158°; ir 1700, 1660, and 1600 cm^{-1}.

Anal. Calcd for $C_{23}H_{15}NO_3$: C, 78.17; H, 4.28; N, 3.96. Found: C, 78.39; H, 4.50; N, 4.06.

Controlled ozonolysis of this compound in dichloromethane gave **1m** as shown by mixture melting point and comparison of the ir spectra.

The yields, melting points, and elemental analyses of compounds **1a–o** are recorded in Table I. The infrared spectra of compounds **1a** show absorption bands at 2950, 1680, 1650, and 1600 cm^{-1}; **1j** at 2950, 1720, 1650 and 1600 cm^{-1}; **1k** (Nujol) at 3000, 1710, 1680, 1650, and 1570 cm^{-1}; **1m** at 3000, 1680, 1650, and 1580 cm^{-1}.

6-Acetyl-5*H*-1-pyrindine-5,7(6*H*)-dione α-Hydrazone.—Hydrazine (0.2 g, 0.00625 mol) was added to a hot solution of **1a** (0.5 g, 0.00265 mol) in ethanol (50 ml). The mixture was quickly chilled in ice and the precipitate was recrystallized from ethanol, giving 0.3 g (55%) of the hydrazone of **1a** as dark orange crystals: mp 265° dec; ir 3350, 3275, 3200, 2950, 1680, 1640, 1580, and 1570 cm^{-1}.

Anal. Calcd. for $C_{10}H_9N_3O_2$: C, 59.10; H, 4.46; N, 20.65. Found: C, 59.18; H, 4.67; N, 21.00.

This hydrazone gives a positive Tollens test and dissolves rapidly in 10% aqueous sodium hydroxide, giving a bright red solution. This behavior is characteristic of 2-acyl-1,3-indandione hydrazones with the hydrazono group on the side chain.[1] The hydrazone of **1a** when treated with dilute hydrochloric acid gives **1a** (ir and mixture melting point).

3-Phenylpyrazolo[3′,4′:3,4]cyclopenta[1,2-b]pyridin-4(1*H*)-one (2a).—To a suspension of **1m** (6.0 g, 0.0239 mol) in anhydrous ethanol (150 ml) was added 95% hydrazine (0.76 g, 0.0239 mol). The red solution was heated at reflux for 12 hr and then cooled to room temperature. The solid was collected by filtration and recrystallized from ethanol to give **2a** in 84% yield as colorless needles: mp 311°; ir 3400, 3100, 2700, 1700 cm^{-1}.

Anal. Calcd. for $C_{15}H_9N_3O$: C, 72.86; H, 3.67; N, 17.00. Found: C, 72.86; H, 3.85; N, 17.27.

Na Salt of 2a.—A mixture of **2a** (1.2 g, 0.00486 mol) and 10% aqueous sodium hydroxide solution (200 ml) was refluxed until a yellow solution was obtained. A little amount of insoluble material was filtered off through a sintered-glass funnel and the filtrate was cooled overnight to give 1 g (77%) of yellow needles: mp >360°; ir 1680, 1640, and 1600 cm^{-1}. No bands appeared in the region between 3500 and 2900 cm^{-1}.

1-Ethyl-3-phenylpyrazolo[3′,4′:3,4]cyclopenta[1,2-b]pyridin-4-one.—A mixture of the sodium salt of **2a** (0.3 g, 0.0012 mol) and a large excess of ethyl bromide in ethanol (25 ml) was refluxed for 5 hr. A little amount of white solid was filtered off and the filtrate was evaporated to dryness. The residue, recrystallized from methanol, gave 0.2 g (65.4%) of yellow, silky needles, mp 168°. The infrared spectrum showed no bands in the 3400–2900-cm^{-1} region.

Anal. Calcd. for $C_{17}H_{13}N_3O$: C, 74.16; H, 4.76; N, 15.26. Found: C, 73.99; H, 4.64; N, 15.36.

3-(*p*-Methoxyphenyl)pyrazolo[3′,4′:3,4]cyclopenta[1,2-b]pyridin-4(1*H*)-one (2b). was obtained as yellow needles, mp 325°, in

(6) Melting points were determined with a Fisher–Johns melting point apparatus, unless otherwise indicated, and are uncorrected. For high melting point compounds a sealed capillary tube in a silicon bath was used. The infrared spectra were recorded on a Baird Model B recording spectrophotometer and on an Infracord spectrophotometer Model 137, using potassium bromide pellets. For the study of the structures of compounds **4** and **5**, the infrared spectra were obtained on Perkin-Elmer Models 221 G and 421 spectrophotometers (potassium bromide pellets). The insolubilities of these compounds in carbon tetrachloride, carbon disulfide, or chloroform made this study very difficult as the intermolecular hydrogen bonding could not be overcome by dilution. Nuclear magnetic resonance spectra were obtained on a Varian A-60A spectrometer, DMSO-d_6 being used as a solvent and TMS as an internal standard. Elemental analyses were performed by Dr. A. Bernhardt, Mikroanalytisches Laboratorium, Max Planck Institute für Kohlenforschung, Mülheim (Ruhr), West Germany.

TABLE I

6-ACYL-5*H*-1-PYRINDINE-5,7(6*H*)-DIONES (1a–o)

Compd	R	Yield, %	Mp, °C	Empirical formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
1a	CH_3	37.2	148	$C_{10}H_7NO_3$	63.49	3.73	7.41	63.72	3.92	7.15
1b	C_2H_5	39.4	149	$C_{11}H_9NO_3$	65.02	4.46	6.89	64.93	4.73	6.61
1c	C_3H_7	32.4	89	$C_{12}H_{11}NO_3$	66.35	5.10	6.45	66.40	5.10	6.36
1d	*i*-C_3H_7	36.0	92	$C_{12}H_{11}NO_3$	66.35	5.10	6.45	66.58	5.29	6.48
1e	C_4H_9	64.2	88	$C_{13}H_{13}NO_3$	67.52	5.67	6.06	67.52	5.63	6.10
1f	*i*-C_4H_9	45.7	101	$C_{13}H_{13}NO_3$	67.52	5.67	6.06	67.62	5.74	6.00
1g	*sec*-C_4H_9	27.2	77	$C_{13}H_{13}NO_3$	67.52	5.67	6.06	67.67	5.57	6.14
1h	C_5H_{11}	50.0	98[a]	$C_{14}H_{15}NO_3$	68.55	6.16	5.71	68.77	6.05	5.72
1i	C_6H_{13}	20.0	88	$C_{15}H_{17}NO_3$	69.48	6.61	5.40	69.33	6.30	5.44
1j	$CH_2C_6H_5$	18.7	139	$C_{16}H_{11}NO_3$	72.44	4.18	5.28	72.47	4.28	5.49
1k	$CH(C_6H_5)_2$	69.0	170	$C_{22}H_{15}NO_3$	77.40	4.43	4.10	77.29	4.43	3.94
1l	C_3H_5[b]	49.0	177	$C_{12}H_9NO_3$	66.97	4.22	6.51	66.96	4.40	6.51
1m	C_6H_5	38.3	188[c,d]	$C_{15}H_9NO_3$	71.71	3.61	5.57	71.53	3.60	5.54
1n	*p*-$OCH_3C_6H_4$[e]	8.4	161[d]	$C_{16}H_{11}NO_4$						
1o	$C_{10}H_7$(1-)	21.6	110	$C_{19}H_{11}NO_3$	75.74	3.68	4.65	76.15	3.69	4.63

[a] Recrystallized from petroleum ether (bp 30–60°). [b] Cyclopropyl group. [c] Recrystallized from methanol. [d] A sealed capillary tube in a silicon bath was used. [e] This compound was not easily purified for analysis. However, the product of the reaction of **1n** with hydrazine, **2b**, gave good analyses.

TABLE II

3-SUBSTITUTED PYRAZOLO[3′,4′:3,4]CYCLOPENTA[1,2-*b*]PYRIDIN-4-(1*H*)-ONE HYDRAZONES (4a–n)

Compd	R	Yield, %	Mp, °C[a]	Ratio of isomers 4:5	Empirical formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
4a	CH_3	68.0	265[b]	8:1	$C_{10}H_9N_5$	60.29	4.55	35.16	60.20	4.71	34.97
4b	C_2H_5	38.0	225[c]	4:1	$C_{11}H_{11}N_5$	61.95	5.20	32.85	62.20	5.22	32.78
4c	C_3H_7	83.5	182[d]	1:0	$C_{12}H_{13}N_5$	63.42	5.77	30.82	63.62	5.63	30.75
4d	*i*-C_3H_7	50.0	200[d]	3:1	$C_{12}H_{13}N_5$	63.42	5.77	30.82	63.70	5.93	30.45
4e	C_4H_9	32.0	164[c]	10:3	$C_{13}H_{15}N_5$	64.71	6.27	29.03	64.85	6.20	28.95
4f	*i*-C_4H_9	36.0	144[c]	3:2	$C_{13}H_{15}N_5$	64.71	6.27	29.03	64.74	5.91	29.05
4g	*sec*-C_4H_9	40.0	185[c]	2:1	$C_{13}H_{15}N_5$	64.71	6.27	29.03	65.00	6.40	28.85
4h	C_5H_{11}	96.0	186[d]	1:0	$C_{14}H_{17}N_5$	65.86	6.71	27.43	66.00	6.61	27.33
4i	C_6H_{13}	48.3	148[d]	1:0	$C_{15}H_{19}N_5$	66.89	7.11	26.00	66.89	7.04	25.94
4j	$CH_2C_6H_5$	48.0	188[d]	4:1	$C_{16}H_{13}N_5$	69.80	4.76	25.44	69.58	5.10	25.61
4k	$CH(C_6H_5)_2$	58.0	193[d]	1:0	$C_{22}H_{17}N_5$	75.19	4.88	19.93	75.35	5.16	19.80
4l	C_3H_5[e]	47.7	210[c]	5:1	$C_{12}H_{11}N_5$	63.98	4.92	31.09	63.66	5.19	30.92
4m	C_6H_5	96.0	240[f]	1:0	$C_{15}H_{11}N_5$	68.95	4.24	26.81	68.71	4.37	25.76[g]
4n	*p*-$OCH_3C_6H_4$	71.0	238[b]	1:0	$C_{16}H_{13}N_5O$	65.97	4.50	24.04	66.20	4.59	23.81

[a] Samples for melting point determinations were heated rapidly, as slow heating causes disproportionation to form the symmetrical azines and hydrazine. [b] Recrystallization solvent: ethanol. [c] Recrystallization solvent: benzene. [d] Recrystallization solvent: benzene–petroluem ether (bp 30–60°). [e] Cyclopropyl group. [f] Recrystallization solvent: ethanol–water. [g] This compound was not easily purified for analysis. However, the Wolff–Kishner reduction of this compound gave a product, **6e**, of good analysis.

90% yield from **1n** and hydrazine following the procedure above described for **2a**. Its infrared spectrum is similar to that of **2a**.

Anal. Calcd for $C_{16}H_{11}N_3O_2$: C, 69.30; H, 4.00; N, 15.16. Found: C, 69.29; H, 4.12; N, 14.94.

3-Substituted Pyrazolo[3′,4′:3,4]cyclopenta[1,2-*b*]pyridin-4-(1*H*)-one Hydrazones (4a–n) and 3-Substituted Pyrazolo[3′,4′:3,4]cyclopenta[2,1-*b*]pyridin-4-(1*H*)-one Hydrazones (5a–h). From Compounds 1.—The general procedure was as follows. To a mixture of the appropriate 6-acyl-5(*H*)-1-pyrindine-5,7(6*H*)-dione (1) (0.00493 mol) and anhydrous ethanol (100 ml) was added 95% hydrazine (0.63 g, 0.0197 mole) and the resulting yellow solution was refluxed for 48 hr. The solvent was evaporated on a steam bath under reduced pressure, the residue was extracted at the boil with benzene, and the suspension was filtered. The filtrate was concentrated and cooled and the precipitated solid was recrystallized from a suitable solvent (see Table II) to give **4a–n** as yellow crystals.

The product, insoluble in benzene, was recrystallized from ethanol or ethanol–water mixtures to give **5a–h** as colorless crystals. In the case of compounds **4a** and **5a** the residue, after evaporation of the solvent, was chromatographed on neutral alumina (elution with chloroform) to give starting material **1a**, compound **4a**, and compound **5a**, in the order indicated. The ir spectra of compounds **4** show bands at 3360, 3150, and 3050 cm^{-1} and those of compounds **5** at 3350, 3220, and 3160 cm^{-1}.

The yields, melting points, and elemental analyses of the hydrazones **4a–n** and **5a–h**, prepared from compounds **1**, are listed in Tables II and III, respectively.

3-Phenylpyrazolo[3′,4′:3,4]cyclopenta[1,2-*b*]pyridine-4(1*H*)-one Hydrazone (4m). From Compound 2a.—A mixture of **2a** (2.48 g, 0.01 mol), 95% hydrazine (0.34 ml), and absolute ethanol (50 ml) was stirred at reflux for 48 hr. The solvent was evaporated under reduced pressure and the yellow residue, completely soluble in hot benzene, was chromatographed on neutral alumina (chloroform as the eluent) to give 2.12 g (81%) of **4m**. The identity of this compound with that obtained directly from **1m** with excess of hydrazine was established by mixture melting point determination and by comparison of the ir spectra. Further elution of the alumina column yielded none of the isomer **5**.

3-(*p*-Methoxyphenyl)pyrazolo[3′,4′:3,4]cyclopenta[1,2-*b*]pyridin-4(1*H*)-one Hydrazone (4n). From Compound 2b.—It was obtained in 88% yield as yellow crystals, following the procedure above described for **4m**. This compound was found identical (mixture melting point and ir) with the compound obtained directly from **1n** and excess hydrazine, as described above.

3-*n*-Amylpyrazolo[3′,4′:3,4]cyclopenta[1,2-*b*]pyridine-4(1*H*)-one azine was obtained in 42.8% yield by heating **4h** in a silicon oil bath at 250° for 15 min. The dark brown mass was recrystallized twice from ethanol to give yellow needles, mp 311° (sealed tube in an oil bath).

Anal. Calcd. for $C_{28}H_{30}N_8$: C, 70.27; H, 6.32; N, 23.42. Found: C, 70.22; H, 6.45; N, 23.21.

3-Phenylpyrazolo[3′,4′:3,4]cyclopenta[1,2-*b*]pyridin-4(1*H*)-one azine was obtained by refluxing for 2 hr a mixture of **4m** (0.5 g, 0.0019 mol) and 25% aqueous hydrochloric acid (15 ml). The resulting red solid (0.35 g, 74.8%) recrystallized from a mixture

TABLE III

3-SUBSTITUTED PYRAZOLO[3′,4′:3,4]CYCLOPENTA[2,1-*b*]PYRIDIN-4(1*H*)-ONE HYDRAZONES (5a–h)

Compd	R	Yield, %	Mp, °C[a]	Empirical Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
5a	CH_3	8.5	281	$C_{10}H_9N_5$	60.29	4.55	35.16	60.07	4.59	35.02
5b	C_2H_5	9.5	250	$C_{11}H_{11}N_5$	61.95	5.20	32.85	61.77	5.15	32.88
5c	*i*-C_3H_7	17.0	233	$C_{12}H_{13}N_5$	63.42	5.77	30.82	63.68	6.10	30.61
5d	C_4H_9	9.6	197	$C_{13}H_{15}N_5$	64.71	6.27	29.03	64.87	6.11	28.82
5e	*i*-C_4H_9	24.0	214	$C_{13}H_{15}N_5$	64.71	6.27	29.03	65.11	6.31	29.00
5f	*sec*-C_4H_9	20.0	196	$C_{13}H_{15}N_5$	64.71	6.27	29.03	64.50	6.28	28.89
5g	$CH_2C_6H_5$	12.0	238	$C_{16}H_{13}N_5$	69.80	4.76	25.44	69.77	5.05	25.41
5h	C_3H_5[b]	9.6	244	$C_{12}H_{11}N_5$	63.98	4.92	31.09	64.13	5.04	30.81

[a] Samples for melting point determinations were heated rapidly, as slow heating causes disproportionation to form the symmetrical azines and hydrazine. [b] Cyclopropyl group.

TABLE IV

3-SUBSTITUTED 1,4-DIHYDROPYRAZOLO[3′,4′:3,4]CYCLOPENTA[1,2-*b*]PYRIDINES (6a–e)

Compd	R	Mp, °C	Empirical formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
6a	*i*-C_3H_7	162[a]	$C_{12}H_{13}N_3$	72.33	6.57	21.09	72.39	6.65	20.78
6b	*sec*-C_4H_9	171[a]	$C_{13}H_{15}N_3$	73.27	7.05	19.78	72.94	6.84	19.93
6c	*n*-C_5H_{11}	155[a]	$C_{14}H_{17}N_3$	74.00	7.54	18.49	74.10	7.60	18.49
6d	$CH(C_6H_5)_2$	272[b,c]	$C_{22}H_{17}N_3$	81.71	5.30	13.00	81.93	5.54	12.80
6e	C_6H_5	300[c,d]	$C_{15}H_{11}N_3$	77.27	4.75	18.02	77.07	4.69	17.89

[a] Recrystallization solvent: benzene–petroleum ether (bp 30–60°). [b] Recrystallization solvent: benzene–methanol. [c] A sealed capillary tube in a silicon bath was used. [d] Recrystallization solvent: acetone.

of benzene and dimethylformamide did not melt up to 360°; ir 3400–3200 and 1620 cm^{-1}.

Anal. Calcd. for $C_{30}H_{18}N_8$: C, 73.45; H, 3.70; N, 22.85. Found: C, 73.32; H, 3.89; N, 22.59.

This azine was also obtained (80% yield) by refluxing for 3 hr a mixture of 1m and 3 equiv of hydrazine in acetic acid. The identity of this azine with that above described was established by ir spectra comparison.

3-Substituted 1,4-Dihydropyrazolo[3′,4′:3,4]cyclopenta[1,2-*b*]-pyridines (6a–e). Procedure A. From Pyrindinediones 1.—A mixture of the appropriate pyrindinedione 1 (0.0088 mol), 95% hydrazine (2.0 ml), and diethylene glycol (40 ml) was heated in an open flask over a 1-hr period to 140°. To the resulting clear yellow solution was added a solution of potassium hydroxide (5.0 g) in diethylene glycol (20 ml), the temperature was raised slowly to 200°, and the mixture was kept at this temperature for 1 hr. The dark red solution was cooled and added with stirring to ice water (200 ml). The precipitate was collected by filtration, washed, and recrystallized from suitable solvent (see Table IV) to give 6a–e as yellow crystals (6d is colorless) in 55–65% yields. In the case of 6a and 6c, after heating at 200°, the cold mixture was poured into water and extracted with ether. The solvent was evaporated and the residue was recrystallized.

Procedure B. From Hydrazones 4.—A mixture of the appropriate hydrazone 4 (0.00383 mol), potassium hydroxide (2.0 g), and diethylene glycol (25 ml) was heated in an open flask over a 2-hr period to 200°. The resulting brown solution was cooled and poured into ice water (100 ml) and the precipitate was recrystallized from suitable solvent (see Table IV) to give 6a–e in 50–60% yields. In the case of 6a and 6c, after heating at 200°, the cold mixture was worked up as described above under A. In the preparation of compound 6b, sodium was used in place of potassium hydroxide and the mixture was heated at 210° for 12 hr, then cooled, acidified with dilute hydrochloric acid, and extracted with benzene. The solvent was removed under reduced pressure and the residue was recrystallized from benzene–petroleum ether.

The melting points and elemental analyses of compounds 6 are recorded in Table IV. The ir spectra show absorption bands in the 3200–2900-, 1600–1580-, 1470–1450-, 1420–1410-, and 1090–1070-cm^{-1} regions. The nmr spectra of 6a and 6b show peaks at δ 3.5 (s, 2 protons) and at δ 8.2, 7.7, and 7.1 ppm. (m, aromatic protons). The compounds prepared according to procedure A were identical with those prepared according to procedure B as shown by mixture melting point determinations and by comparison of the infrared spectra.

1,4-Dihydro-3-isopropylpyrazolo[3′,4′:3,4]cyclopenta[2,1-*b*]-pyridine (7a).—A mixture of hydrazone 5c (2.0 g), sodium (2.0 g), and diethylene glycol (70 ml) was heated at 210° for 12 hr, then cooled, acidified with dilute hydrochloric acid, and extracted with benzene. Removal of benzene under reduced pressure and crystallization of the residue from benzene–petroleum ether gave 7a (45% yield) as yellow crystals, mp 167°; nmr shows peaks at δ 3.3 (s, 2 protons) and at δ 8.2, 7.7, and 7.1 ppm (m, aromatic protons).

Anal. Calcd for $C_{12}H_{13}N_3$: C, 72.33; H, 6.57; N, 21.10. Found: C, 72.00; H, 6.67; N, 20.97.

3-*sec*-Butyl-1,4-dihydropyrazolo[3′,4′:3,4]cyclopenta[2,1-*b*]-pyridine (7b) was obtained in 48% yield from hydrazone 5f, following the above procedure for 7a, as yellow crystals, mp 178°; the nmr spectrum is similar to that of compound 7a.

Anal. Calcd. for $C_{13}H_{15}N_3$: C, 73.27; H, 7.05; N, 19.78. Found: C, 73.06; H, 6.90; N, 19.64.

Registry No.—**1a**, 32121-10-1; **1b**, 32121-11-2; **1c**, 32121-12-3; **1d**, 32121-13-4; **1e**, 32121-14-5; **1f**, 32121-15-6; **1g**, 32121-16-7; **1h**, 32121-17-8; **1i**, 32111-61-8; **1j**, 32111-62-9; **1k**, 32111-63-0; **1l**, 32111-64-1; **1m**, 32111-65-2; **1n**, 322207-46-8; **1o**, 32111-66-3; **2a**, 32111-67-4; 2a Na salt, 32111-68-5; **2b**, 32111-69-6; **4a**, 32111-70-9; **4b**, 32111-35-6; **4c**, 32111-36-7; **4d**, 32111-37-8; **4e**, 32111-38-9; **4f**, 32207-33-3; **4g**, 32207-34-4; **4h**, 32111-39-0; **4i**, 32111-40-3; **4j**, 32111-41-4; **4k**, 32111-42-5; **4l**, 32111-43-6; **4m**, 32111-44-7; **4n**, 32111-45-8; **5a**, 32111-46-9; **5b**, 32207-35-5; **5c**, 32110-91-1; **5d**, 32110-92-2; **5e**, 32110-93-3; **5f**, 32110-94-4; **5g**, 32110-95-5; **5h**, 32110-96-6; **6a**, 32110-97-7; **6b**, 32110-98-8; **6c**, 32110-99-9; **6d**, 32111-00-5; **6e**, 32111-01-6; **7a**, 32111-02-7; **7b**, 32111-03-8; hydrazine, 302-01-2; 6-acetyl-5*H*-1-pyrindine-5,7(6*H*)-dione α-hydrazone, 32120-78-8; 1-ethyl-3-phenylpyrazolo[3′,4′:3,4]cyclopenta[1,2-*b*]pyridin-4-one, 32120-79-9; 3-*n*-amylpyrazolo[3′4′:3,4]-cyclopenta[1,2-*b*]pyridin-4(1*H*)-one azine, 32256-03-4; 3-phenylpyrazolo[3′,4′:3,4]cyclopenta[1,2-*b*]pyridin-4(1*H*)one azine, 32120-80-2.

Acknowledgment.—We gratefully acknowledge the valuable assistance of Dr. Mario Sartori in connection with this research.

Contribution to the Cyclization of Hydrazones of α,β-Unsaturated Carbonyl Compounds. The Biscarbamyl- and Bisthiocarbamylhydrazones of Malondialdehyde

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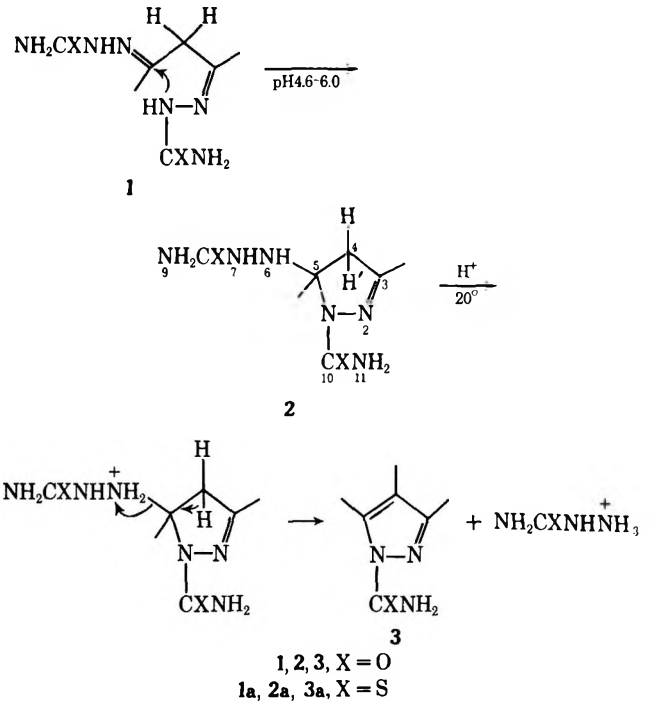
Received April 12, 1971

The symmetrical bissemicarbazone of malonaldehyde **1** readily cyclized during its preparation to form the isomeric semicarbazido-substituted carbamylpyrazoline **2**. The cyclization proceeded by nucleophilic addition of the acidic hydrazine nitrogen in one semicarbazone group to the polarized azomethine (imine) double bond ($-N^{-\delta}=^{+\delta}C<$) in the adjacent group. The thiosemicarbazone of malonaldehyde **1a** reacted similarly to form a thiosemicarbazido-substituted thiocarbamylpyrazoline **2a**. In a suspension of water at 20°, increasing hydrogen ion concentrations catalyzed elimination of the semicarbazido or thiosemicarbazido substituents with the formation of pyrazole-1-carboxamide (**3**) or pyrazole-1-thiocarboxamide (**3a**).

In the course of our studies concerning reactions of malondialdehyde with various nitrogenous bases, we reexamined the structures of a number of known products of this compound. Reaction of phenyl-[1] or dinitrophenylhydrazine,[2] hydrazine, semicarbazide,[3] or thiosemicarbazide[4] with tetraalkoxypropanes gave the corresponding 1-substituted pyrazoles as reported. Although the semicarbazones and phenylhydrazones of α,β-unsaturated aldehydes and ketones have provided a convenient route to the substituted 2-pyrazolines[5,6] and the cyclization of monohydrazones of 1,3 diketones leading to the formation of pyrazoline and pyrazole has recently been described,[7] the formation of substituted pyrazolines from bishydrazones of 1,3-dialdehydes have not been reported previously. Neither has the formation of the known 1-substituted pyrazoles[1-4] been considered to proceed *via* the respective pyrazoline intermediates. Earlier attempts to obtain the semicarbazones of 1:1 condensation products of malonaldehyde and various amino acids gave a single, difficultly soluble product on each occasion, which best analyzed for the bissemicarbazone of malonaldehyde,[8] previously described by L. Claisen's laboratory in 1904.[9]

SCHEME I



Results and Discussion

Reaction of the semicarbazide HCl with malondialdehyde in aqueous acetate buffer, pH 4.6, gave a white crystalline product which analyzed ($C_5H_{10}O_2N_6$) for the expected bissemicarbazone of malondialdehyde **1** (Scheme I). Under more acidic conditions the principal product isolated was pyrazole-1-carboxamide **3**. Further, heating of the so-called bissemicarbazone to 135° gave a sublimate consisting predominantly of pyrazole and traces of **3** which were readily identified from their nmr and mass spectra. However, initial nmr data did not provide the expected evidence for the chemically equivalent methylene protons of the open-chain bissemicarbazone structure **1** nor any evidence for the conjugated form of **1**.

Direct evidence in support of the pyrazoline structure **2** for the bissemicarbazone of malondialdehyde was obtained from the 100-MHz nmr spectrum in D_2O given in Figure 1, where chemical shifts are expressed in parts per million from *tert*-butyl alcohol, δ 1.28 from TMS. The azomethine proton H_3 appeared as a closely spaced quartet at 5.8 ppm and H_5, centered at 4.0 ppm, was also a quartet. The geminal protons, H_4 and $H_{4'}$, constitute the AB part of an ABMX pattern and appeared as two octets to high field with calculated chemical shifts of 1.57 and 1.96 ppm, respectively. The geminal coupling constant of −19.5 Hz was close to that reported for a number of substituted pyrazolines.[10] The geminal coupling constant $J_{4,4'}$ was assumed to be negative since this seems to be in keeping with experimental values for sp^3-hybridized groups and since the magnitude of geminal coupling in five-membered ring systems becomes more negative, in the range of −(16–17 Hz), if the nonequivalent methylene protons are adjacent to a π system.[11] $H_{4'}$ was assigned the high-

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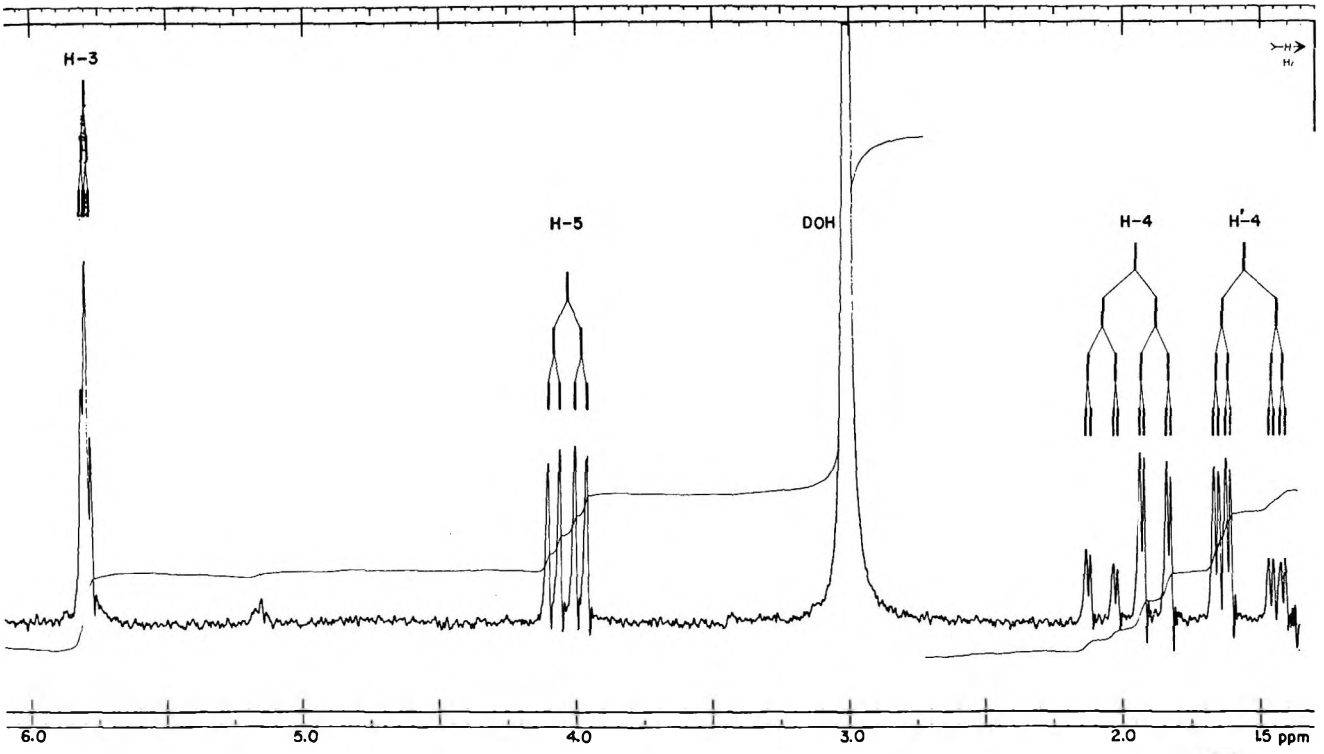

Figure 1.—Nmr spectrum of 2 in D_2O at 60°, 100 MHz, chemical shift from *tert*-butyl alcohol, δ 1.28 from TMS.

field multiplet due to shielding by H_5 with which it has a smaller coupling constant, $J_{4',5} = 4.0$ Hz, by comparison to H_4 which by virtue of its transdiaxial disposition to H_5 had a $J_{4,5}$ of 10.0 Hz. The 100-MHz nmr spectrum of 2 in dimethyl sulfoxide-d_6 (DMSO-d_6) gave, on the addition of a drop of pyridine-d_5, H_5 and H_6 as a multiplet, at δ 5.4 ppm composed of H_5, a sextet, which was partly obscured by the doublet of H_6. Coupling between H_5 and H_6 was ~5 Hz. On the addition of D_2O, H_6 exchanged out rapidly and H_5 collapsed to a quartet. HCNH coupling is observed only in those cases where proton exchange is sufficiently slow.[12] Presumably, in the absence of a trace of pyridine there was sufficient acid present to promote rapid exchange of the NH protons since H_6 appeared as a singlet and H_5 as a poorly resolved quartet in pure DMSO-d_6. H_7 was assigned to the sharp singlet at δ 7.5 ppm while H_9,$H_{9'}$ and H_{11},$H_{11'}$ were assigned to singlets at δ 6.7 and 6.3 ppm, respectively. H_3 was represented by a singlet at δ 7.1 and the geminal protons H_4 and $H_{4'}$ appeared very similarly to the 16-line pattern described in Figure 1.

The 100-MHz nmr spectrum of 2a in DMSO-d_6 corroborated evidence provided from the mass spectrum in support of its structural assignment. H_3 appeared as a poorly resolved triplet, δ 7.6 ppm, while H_4 and $H_{4'}$ had a geminal coupling constant of −18.0 Hz. H_4 was partially obscured by the DOH signal. H_5 appeared as a six-line multiplet and was composed of 4-Hz coupling each to H_6 and $H_{4'}$ and 10-Hz coupling to H_4. H_7 appeared as a sharp singlet, δ 9.0 ppm, and H_9 and $H_{9'}$ as nonequivalent broadened peaks at δ 8.4 and ~8.2 ppm, respectively. On the addition of D_2O, H_6 exchanged out and H_5 collapsed to the expected quartet.

Due to a greater contribution of the dipolar resonance form $^-S—C{=}N^+<$ to their ground states, thioamides display significantly greater barriers to rotation about the C–N bond than do their corresponding amides.[13] As a consequence, *N*-alkyl substituents show magnetic nonequivalence[14] and, for those cases reported, the substituents syn to sulfur were assigned to higher field signals. Assignment of $H_{9'}$ to the high field of H_9 was tentative and made by analogy to the assignments for alkyl substituents.

H_{11} and $H_{11'}$ showed chemical shift equivalence and formed a broad singlet centered at δ 8.0 ppm and supported the suggestion that the ring π electrons contributed more effectively to the dipolar character of the 1-thione substituent than did the nitrogen carrying H_{11} and $H_{11'}$. Although restricted rotation about the thione–N bond in substituted thioureas has been reported,[15] no account of restricted rotation about the C–N bond in unsubstituted thioamides has appeared previously.

Fragmentation of 2 in the mass spectrometer went according to Schemes II and III and is supported where indicated by the corresponding metastable peaks (m*). The mass spectrum was devoid of the parent ion *m/e* 186, and the expected ion for the fragmentation of aliphatic semicarbazones, $NH_2CONH^+N{\equiv}CH$, *m/e* 86,[16] was conspicuous for its low (2%) abundance. Instead the mass spectrum bore a striking resemblance to that for pyrazole carboxamide 3. The highest mass fragments and base peaks occurred at 112 and 69 for the so-called bissemicarbazone and 111 and 68 for the pyrazole carboxamide.

Initial uncertainty as to the mode of fragmentation

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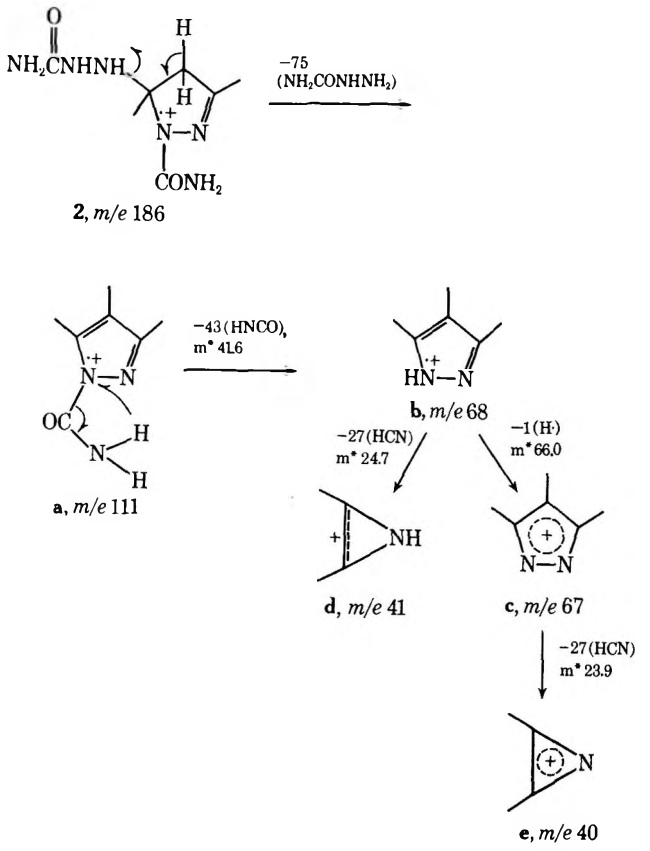
SCHEME II



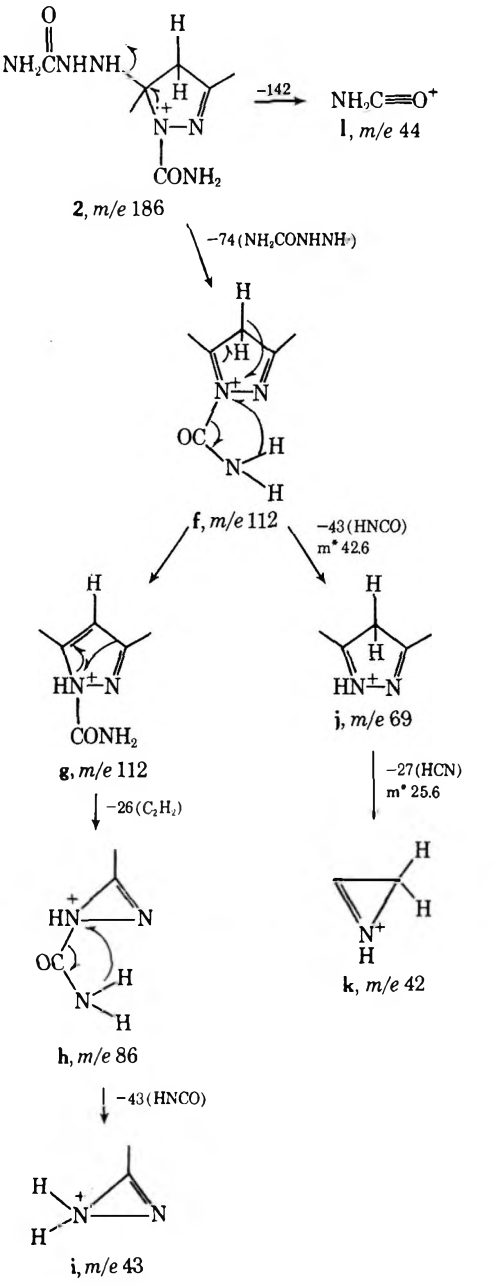
existed also due to the fact that 2 could give rise to *m/e* 111 (a) by thermal degradation or the molecular ion of 2 could lose semicarbazide *m/e* 75 as a neutral fragment on electron impact ($M\cdot^+ - 75 = 111$). The latter process was favored as the ratios *m/e* 112/111 and *m/e* 69/68 were not significantly altered by source temperatures between 130 and 320°.

Fragmentation arising from charge localization on the heterocyclic ring generated ions by two paths. The first (Scheme II), by loss of a neutral semicarbazide fragment, produced *m/e* 111 (a) and by subsequent loss of HNCO gave *m/e* 68 (b) which by either the loss of HCN or hydrogen gave **d** or **c**, respectively. The latter ion *m/e* 67 subsequently lost 27 mass units (HCN) to give **e**.

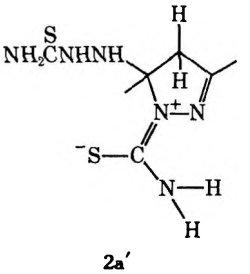
The structure of the highest mass fragment *m/e* 112 (**f**) (Scheme III) in the spectrum was inferred by its transformation to the base peak *m/e* 69 (**j**) by way of the loss of a neutral HNCO fragment and the most intense metastable ion (m* 42.6) in the spectrum confirmed this transition. Although the loss of the $NH_2CONHNH\cdot$ radical was not observed in the mass spectra of the semicarbazones previously examined,[16] it along with ion **f** would be expected to make up the major fragmentation product of 2. No metastable ions were observed in support of the transitions **f** → **g** → **h** → **i**. The structures **h** and **i** were proposed for *m/e* 86 and 43 rather than $NH_2CONHN^+{\equiv}CH$ and $NH_2N^+{\equiv}CH$ to be more consistent with the proposed pyrazoline structure 2 rather than the open chain bissemicarbazone **1**. The ion **l** of mass 44 was also present in the spectra of semicarbazones of aliphatic aldehydes and ketones as a result of amide cleavage.[16]

The mass spectrum of **2a** differed in several significant respects from that of 2. The molecular ion *m/e*

SCHEME III



218 for **2a** was observed and the pyrazolium (*m/e* 68) rather than the pyrazolinium (*m/e* 69) ion constituted the base peak. Although thermal degradation could account for the *m/e* 127 ($M\cdot^+ - 91$) and *m/e* 91 ($NH_2CSNHNH_2$) ions, only about half of the pyrazole (*m/e* 68) ion could arise from this source in the extreme, as the ratio *m/e* 127/68 in pyrazole-1-thiocarboxamide (**3a**) was 0.5. These differences might be rationalized on the basis of the possible contribution of the dipolar resonance form **2a′** to the ground state of **2a**, thus di-



2a′

minishing the tendency for charge localization on the heterocyclic ring of the molecular ion. Consequently, charge localization on either ring substituent is favored and fragmentation proceeds by the loss of thiosemicarbazide as both a neutral fragment giving *m/e* 127 and a radical ion (*m/e* 91).

Experimental Section

Melting points were determined microscopically on a hot stage. Nmr spectra were recorded with a Varian HA-100 instrument, and, for mass spectral analysis, a Nuclide 12-90-G mass spectrometer with a direct insertion probe, source temperature 240°, 70 eV, and 100-μA trap current was used.

5-Semicarbazido-1-carbamyl-2-pyrazoline (2).—A solution containing 4.95 g of sodium acetate and 3.34 g (0.03 mol) of semicarbazide HCl in 18 ml of water was made up. Malonaldehyde (β-hydroxyacrolein) was then prepared by hydrolyzing 3.1 g (0.014 mol) of 1,1,3,3-tetraethoxypropane with 1.5 ml of 1 *N* HCl at 45–50°, for about 20 min, until the solution was miscible and clear. The malonaldehyde and the buffered semicarbazide solutions were mixed (pH 4.6) and heated monentarily in a boiling water bath, and the reaction mixture was then left overnight at room temperature. The white crystals (1.6 g) which formed had a two-stage melting point, *i.e.*, a rearrangement (see Pyrazole, B), melting, and resolidification took place quite sharply and reproducibly at 208–210° and, upon further heating, the compound melted at 248–250°. Recrystallization was carried out from saturated hot water solutions: yield 61.5%; uv max (H_2O) 234 nm (ϵ 8150) at pH 6.0; ^{1}H nmr (D_2O, 60°), lock signal *tert*-butyl alcohol (δ 1.28 from TMS), δ 7.08 (t, 1 H, $J_{3,4'}$ = 1.6, $J_{3,4}$ = 1.2 Hz, H-3), 5.28 (qt, 1 H, $J_{5,4}$ = 10.0, $J_{5,4'}$ = 4.0 Hz, H-5), 3.26 midpoint, 3.24 calcd (8-line pattern, 1 H, gem $J_{4,4'}$ = −19.5, $J_{4,5}$ = 10.0, $J_{4,3}$ = 1.2 Hz, H-4), 2.82 midpoint, 2.85 calcd (8-line pattern, 1 H, gem $J_{4',4}$ = −19.5, $J_{4',5}$ = 4.0, $J_{4',3}$ = 1.6 Hz, H′-4) (relative intensities of inner and outer lines of overall 16-line pattern calcd[11] 1:2.6); ^{1}H nmr (DMSO-d_6, 10% pyridine-d_5, 31.5°) δ 7.46 (s, 1, NH of hydrazine, H-7), 7.08 (s, unresolved triplet, 1, CH, H-3), 6.72 (s, 2, NH of amide, H-9 and H′-9), 6.32 (s, 2, NH of amide, H-11 and H′-11), 5.50 (d, 1, NH of hydrazine, H-6), 5.33 (m, 1 H, H-5), 3.28 (center of 8-line pattern, 1 H, $J_{4,4'}$ = −18 Hz, H-4), 2.95 (center of 8-line pattern, 1 H, $J_{4',4}$ = −18 Hz, H′-4) (relative intensities of inner and outer lines of overall 16-line pattern 1:2.6); mass spectrum (70 eV) *m/e* (rel intensity) 112 (18), 111 (2), 86 (3), 76 (2), 75 (10), 70 (7), 69 (100), 68 (45), 67 (4), 60 (2), 59 (2), 58 (3), 55 (3), 54 (4), 52 (3), 44 (25), 43 (43), 42 (43), 41 (14), 40 (7), 39 (7), 38 (2).

Anal. Calcd for $C_5H_{10}N_6O_2$: C, 32.23; H, 5.41; N, 45.14. Found: C, 32.25; H, 5.35; N, 45.17.

During the crystallization of the pyrazoline, a further 0.2 g of an unidentified yellow product cocrystallized, mp 257°.

Pyrazole-1-carboxamide (3).—Acid-catalyzed conversion of the pyrazoline derivative to pyrazolecarboxamide was achieved by suspending 2 in a small amount of water and by titrating it with 1 *N* HCl. On addition of a few drops of acid with stirring, 2 dissolved and after a few minutes rod-like crystals precipitated. The newly formed compound 3, mp 142–145°, sublimed at 70–80° to an air-cooled cold finger or could be recrystallized from hot water: mp 141° (corr); yield 70%; uv max (H_2O) 234 nm (ϵ 9180) at pH 6.0; ^{1}H nmr (DMSO-d_6–$CDCl_3$, 3:1), from TMS, δ 8.26 (qt, 1 H, $J_{5,4}$ = 2.6, $J_{5,3}$ = 0.8 Hz, H-5), 7.70 (qt, 1 H, $J_{3,4}$ = 1.5, $J_{3,5}$ = 0.8 Hz, H-3), 6.47 (qt, 1 H, $J_{4,5}$ = 2.6, $J_{4,3}$ = 1.5 Hz, H-4), amide protons exchanged with D_2O; mass spectrum *m/e* (rel intensity) 111 M^+ (7), 69 (6), 68 (100), 67 (14), 44 (12), 43 (35), 42 (10), 41 (50), 40 (21), 39 (13), 38 (9).

Pyrazole. A.—When the pyrazoline 2 was heated to 135° in a sublimation apparatus at 1 atm, long, flat needles, mp 64–66°, were deposited on the air-cooled condenser and a brown residue remained. Recrystallizations of the sublimate from *n*-heptane yielded a product, mp 68–69°. For comparative purposes, pyrazole was also prepared from hydrazine HCl and malonaldehyde: mp 69–70°;[3] uv max (H_2O) 210 nm (ϵ 3520) at pH 6.0; ^{1}H nmr ($CDCl_3$), from TMS, δ 6.28 (t, 1 H, $J_{4,3}$ = 2.0, $J_{4,5}$ = 2.0 Hz, H-4), 7.55 (d, 2 H, $J_{5,4}$ and $J_{3,4}$ = 2.0 Hz, H-3 and H-5), 11.92 (s, 1 H, HN); mass spectrum *m/e* (rel intensity) 68 M^+ (100), 69 (8), 67 (15), 42 (9), 41 (50), 40 (29), 39 (19), 38 (12), 37 (5).

B.—When the pyrazoline 2 was heated at 205° for 0.5 hr in a sealed, evacuated tube about 5% of pyrazole was formed. The remaining white solid, mp 262°, was only sparingly soluble in hot water and other solvents; however, 20% solutions could be prepared in 70% perchloric acid; this product was therefore not further analyzed. Pyrazole-1-carboxamide by itself will, however, sublime quite readily, at atmospheric pressure or under vacuum and no decomposition was evident.

5-Thiosemicarbazido-1-thiocarbamyl-2-pyrazoline (2a).—A suspension consisting of 2.73 g (0.03 mol) of thiosemicarbazide and 10 ml of water was prepared. In a separate flask was hydrolyzed 3.1 g (0.014 mol) of 1,1,3,3-tetraethoxypropane with 1.5 ml of 1 *N* HCl at 50°, for about 20 min, until the solution was miscible and a clear yellow. To the hydrolyzed acetal was added 1.0 ml of 2.0 *N* NaOH, and the solution was adjusted to pH 4.5–4.6 and added to the thiosemicarbazide suspension. A tan-colored flocculent precipitate formed with slow dissolution of the remaining thiosemicarbazide. After standing overnight at room temperature, the suspension was cooled in ice and filtered. The dried material (40–50%) was recrystallized two times from a boiling water solution. On cooling, feather-like, light brown-yellow crystals formed: mp 159–161°; uv max (H_2O) 237 nm (ϵ 1.9 × 10^4), 264 (1.7 × 10^4) at pH 6.0; ^{1}H nmr (DMSO-d_6, 31.5°) δ 8.96 (s, 1, NH of hydrazine, H-7), 8.43 (s, 1, NH of amide, H-9), 8.00 (s, 3, NH of amides, H′-9, H-11, and H′-11), 7.60 (s, unresolved triplet, 1 H, H-3), 6.19 (d, 1, NH of hydrazine, H-6), 5.83 (m, 1 H, H-5), 3.58 (center of 8-line pattern, 1 H, $J_{4,4'}$ = −18 Hz, H-4), 3.13 (center of 8-line pattern, 1 H, $J_{4',4}$ = −18 Hz, H′-4) (relative intensities of inner and outer lines of overall 16-line pattern 1:2.2); mass spectrum *m/e* (rel intensity) 218 M^+ (6), 128 (10), 127 (21), 102 (12), 91 (57), 75 (6), 69 (29), 68 (100), 67 (13), 61 (8), 60 (32), 59 (54), 58 (7), 57 (5), 43 (14), 42 (39), 41 (38), 40 (19).

Anal. Calcd for $C_5H_{10}N_6S_2$: C, 27.28; H, 4.81; N, 38.45; S, 29.23. Found: C, 27.50; H, 4.62; N, 38.50; S, 29.37.

Pyrazole-1-thiocarboxamide (3a).—Treatment of 2a in 2 *N* HCl on a steam bath (10 min) gave pyrazole-1-thiocarboxamide: mp 140°; uv max (H_2O) 256 nm (ϵ 6400), 285 (1.0 × 10^4); uv max (EtOH) 252 nm (ϵ 7900), 291 (1.1 × 10^4); ^{1}H nmr (DMSO-d_6–$CDCl_3$, 1:1), from TMS, δ 8.65 (qt, 1 H, $J_{5,4}$ = 2.7, $J_{5,3}$ = 0.7 Hz, H-5), 7.68 (qt, 1 H, $J_{3,4}$ = 1.4, $J_{3,5}$ = 0.6 Hz, H-3), 6.40 (qt, 1 H, $J_{4,5}$ = 2.7, $J_{4,3}$ = 1.4 Hz, H-4), 10.00 and 8.80 (broad singlet peaks, amide protons, NH); mass spectrum *m/e* (rel intensity) 127 M^+ (45), 69 (22), 68 (100), 67 (16), 60 (23), 59 (16), 57 (8), 56 (5), 55 (7), 45 (5), 44 (4), 43 (5), 42 (12), 41 (80), 40 (17), 39 (16), 38 (8).

Registry No.—2, 31819-63-3; 2a, 31819-64-4; 3, 931-08-8; 3a, 1794-34-9.

Resin Acids. XXII. An Unusual Decarboxylation Induced by a Degenerate Acyloin Rearrangement[1,2]

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Received May 13, 1971

Pyrolysis of a dihydroxylactone **2b**, prepared by oxidation of the levopimaric acid–formaldehyde adduct **1**, unexpectedly resulted in decarboxylation to methyl 13α-hydroxy-14-oxoabietan-18-oate (**5**) or to methyl 8α,14α-dihydroxy-12-abieten-18-oate (**8**) depending on the conditions. Decarboxylation of methyl 12α-carboxy-13α-hydroxy-14-oxoabietan-18-oate (**4a**) also gave **5**. These remarkable and unusually facile decarboxylations were traced to a degenerate acyloin rearrangement in 13-hydroxy-14-oxoabietanes which involves reversible migration of the C-12–C-13 and C-8–C-13 bonds. In the methyl ester **4b**, prepared by treatment of **2b** with methanolic HCl, the stable orientation of the carbomethoxy group was shown to be axial. Transformations of **5** and **8** which shed light on the stereochemistry of various 14-oxygenated abietanes are described.

In the preceding paper[1] we reported *inter alia* the unusual oxidation of the levopimaric acid–formaldehyde adduct **1** to the dihydroxylactone **2b**. When we subsequently attempted to assay the utility of **2** as a potential intermediate for the partial synthesis of other terpenoids, we discovered a seemingly unprecedented decarboxylation reaction which eventually could be traced to the existence of a degenerate acyloin rearrangement involving the transitory formation of a β-keto acid. These findings are described in the present communication. We also report the transformation of **2** to a number of 14-oxygenated abietanes by methods which shed light on the stereochemistry of previously reported compounds.

For realization of our initial objective we proposed to hydrolyze **2b** to **3a** and carry out a decarboxylation after oxidation and dehydration of **3a**. However, **3a** could not be isolated because of spontaneous relactonization to **2b**. Hence **2b** was exposed to methanolic hydrogen chloride in the expectation that diester **3b** would be formed. Instead, however, acid-catalyzed cleavage of the lactone function followed by pinacol rearrangement[3] and subsequent methylation with methanolic hydrogen chloride resulted in quantitative conversion of **2b** to a compound **4b**.[4] The infrared spectrum of this substance revealed the absence of the lactone function, but had three carbonyl bands at 1740, 1730, and 1710 cm^{-1}, the first two of which were due to carbomethoxy groups (nmr spectrum). That the third carbonyl band of 1710 cm^{-1} arose from a ketone group was clear from the CD curve, which exhibited the typical n–π^* transition at 284 nm. The presence of a single tertiary hydroxyl group was indicated by a sharp one-proton nmr peak at 3.88 ppm which disappeared on D_2O exchange, and, in contrast to the situation prevailing in the precursors **1** and **2**,[1] the doublets of the isopropyl group were now widely separated, one of them being highly shielded (0.64 ppm).

While it was more than reasonable to assume that the configuration of the 13-hydroxyl and the isopropyl group had not been affected during the conversion of **2b** to **4b**, the stereochemistry at the two centers C-8 and C-12 which *were* involved demanded further study. As regards the configuration at C-8, exposure of **4b** to epimerizing conditions ($NaOH–CH_3OH$) resulted after remethylation with diazomethane in recovery of starting material accompanied by a small amount of **5**,[5] thus indicating that **4b** possessed the stable trans–anti–trans perhydrophenanthrene ring system. The strongly negative Cotton effect of **4b** ($a = -212$) was in accord with this conclusion.

The appearance of the H-12 resonance (slightly distorted triplet at 3.4 ppm) served as a means for investigating the orientation of the carbomethoxy group at C-12. The observed splitting (3 Hz) clearly excluded axial–axial coupling of H-12 to one of its neighbors at C-11 and led to the rather surprising conclusion that the carbomethoxy group was axial, in spite of its stability under epimerizing conditions. Such failure to epimerize under the influence of $NaOH–CH_3OH$ could be due either to the inability of the base to abstract H-12 or to the presence of potentially unfavorable interactions encountered by an equatorial carbomethoxy group, whatever its configuration, the equilibrium in favor of an axial orientation being reinforced by the 3-alkyl ketone effect. The ambiguity was resolved by subjecting **4b** to the action of $NaOD–CH_3OD$. In the recovered **4b**, H-12 had been completely replaced by deuterium as evidenced by the disappearance of the signal at 3.4 ppm. Hence the carbomethoxy group of **4b** prefers the axial orientation.[6]

However, this by no means settles the absolute configuration at C-12, since the requirement for an axial carbomethoxy group is satisfied by two structures: (1) **4b** with ring C in the usual chair conformation and the carbomethoxy group α as in **4A**; (2) **4′b** with ring C in the twist conformation and the carbomethoxy group β as in **4B**. If ring C were a chair, the greater

(1) Previous paper: W. Herz and V. Baburao, *J. Org. Chem.*, **36**, 3271 (1971).

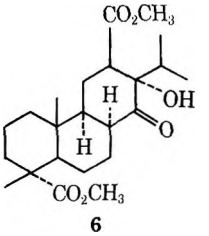
(2) Supported in part by a grant from the National Science Foundation (GP-12582).

(3) For similar hydride shifts in epoxides and glycols derived from Diels–Alder adducts of levopimaric acid, see (a) W. Herz, R. N. Mirrington, H. Young, and Y. Y. Lin, *J. Org. Chem.*, **33**, 4210 (1968); (b) W. Herz and R. C. Blackstone, *ibid.*, **34**, 1257 (1969).

(4) To substantiate the postulated last step, acid **4a**, prepared by cautious basic hydrolysis of **4b**, was reconverted to **4b** by the action of methanol–HCl.

(5) Structure assignment and mode of formation of this substance will be discussed subsequently.

(6) With the carbomethoxy group shown to be axial, the formal argument that in **4b** a cis B/C ring fusion might for some reason be more stable than a trans B/C junction could be discounted, since this would lead to formula **6** which can be dismissed because of the prohibitive interactions (model) and the negative Cotton effect.



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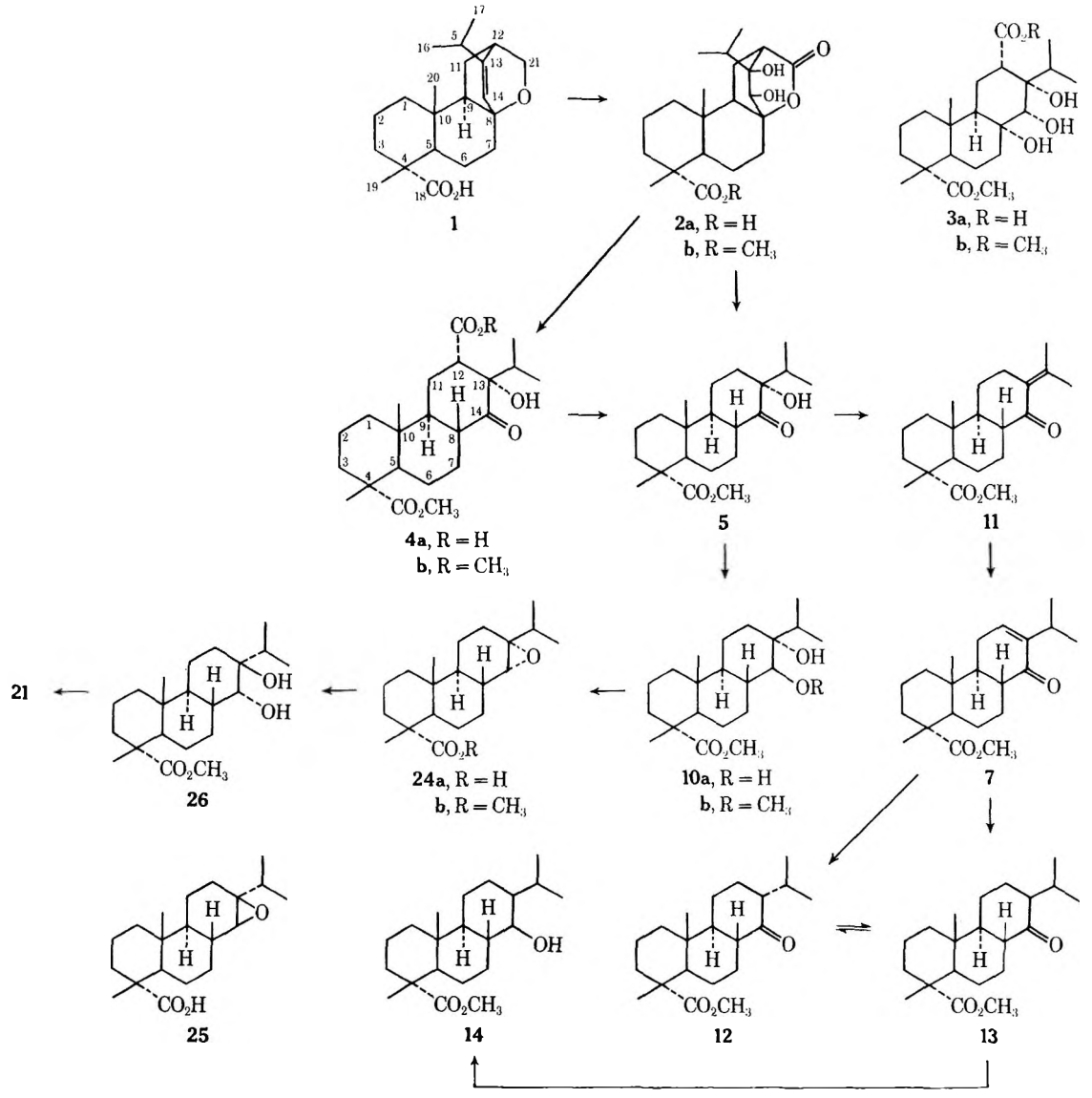
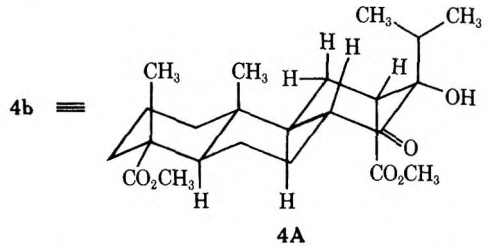
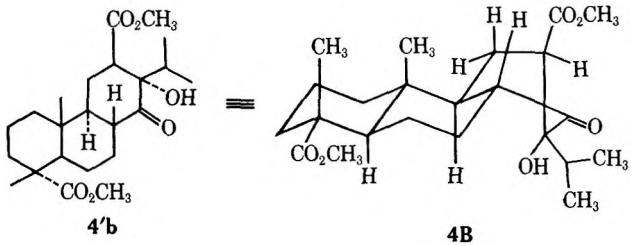


thermodynamic stability of **4b** (CO_2Me axial) over **4'b** (CO_2Me equatorial) would have to be attributed to the difference between one 1,3-diaxial H–CO_2Me interaction in **4b** on the one hand and the sum of one 1,3-H,H, and one skew CO_2Me–isopropyl interaction in **4'b** on the other. If ring C were in the flexible conformation, the greater stability of **4'b** (CO_2Me axial) over **4b** (CO_2Me equatorial) would have to be attributed to a rather tenuous difference between a H–CO_2Me flagpole interaction, reduced by twisting, in **4'b** on the one hand and the sum of a H–H flagpole (also reduced by twisting) and a skew CO_2Me–OH interaction of **4b** on the other.





We prefer **4A**, and hence configuration **4b**, on the following grounds. (1) **4b**, **5**, and **13** (*vide infra*) possess strongly negative Cotton effects of the same magnitude ($a = -212, -207$, and -172). Also the chemical shifts of their C-10 methyl and isopropyl methyl signals are almost identical (see Experimental Section). This suggests that the conformations of **4b**, **5**, and **13** are very similar, if not identical, and that conformational equilibria are not significantly affected by the presence or absence of the carbomethoxy group at C-12 and the α-hydroxyl group at C-13. (2) Conformations corresponding to **4B** would be expected to display considerably weaker Cotton effects than are actually observed.[7,8] (3) In conformations corresponding to **4B**

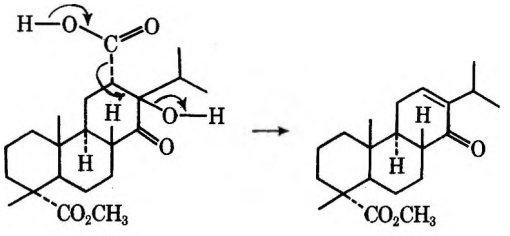
(7) On the other hand, if ring C were in a twist conformation, the "anti-octant" behavior of the hydroxyl group,[8] situated in a positive octant, might conceivably account for the amplitude drop in going from **5** to **13**. *A priori*, no appreciable change in amplitude would be expected if ring C were a chair. However, the drop and the simultaneous decrease in nonequivalence of the isopropyl methyls (see footnote 9) could easily be traced to a slight distortion of ring C of **13**, made now possible by the absence of the hydroxyl function to accommodate the axial isopropyl group.

(8) L. Bartlett, D. N. Kirk, W. Klyne, S. R. Wallis, H. Erdtman, and S. Thorén, *J. Chem. Soc.*, 2678 (1970).

the isopropyl methyls would not be expected to exhibit the degree of nonequivalence actually manifested in the nmr spectra of **4b**, **5**, and **13**, whereas models of structures corresponding to **4A** reveal that in the more heavily populated rotamers one of the methyl group is above and in the shielding cone of the ketone group in accordance with experimental observations.[9,10] (4) Lastly we note that **5** and **13** are reduced facilely by sodium borohydride in methanol at room temperature, hydride attack occurring exclusively from the α side, to give **10a** and **14** (*vide infra*). By contrast, **4b** is not reduced under these conditions, a result explicable on the basis of formula **4A**, where the axial and α oriented carbomethoxy group interferes with reagent approach from the α side, but not on the basis of formula **4B**.[11]

Thermal decarboxylation of **4a** was expected to provide the enone **7** by the process adumbrated in Scheme I.[12] However, the product, isolated in 70% yield by

SCHEME I



4a **7**

heating at 280°, was not **7**, but **5**, the minor product encountered earlier during the attempt to epimerize **4b**.[13] Some of the properties of this substance have been mentioned previously; the presence of strong intramolecular hydrogen bonding, the stability toward base, the ORD curve, and the similarity of its nmr spectrum to that of **4b** are entirely in agreement with its formulation as methyl 13α-hydroxy-14-oxoabietan-18-oate.[14]

The unexpectedly facile decarboxylation of **4a** to **5**, whose mechanism will be discussed subsequently, suggested that a thermal process involving intramolecular hydroxyl proton abstraction by the lactone ether oxygen of **2b** as illustrated in Scheme II (path a) might initiate rearrangement of **2b** to **4a** or its anion and that this would be followed by decarboxylation to **5**. This expectation was borne out in practice. When **2b** was heated to 280° for 10 min, two crystalline substances were isolated after column chromatography. The less polar compound (30% yield) was **5**; the more polar compound was shown to be **8** on the following grounds.

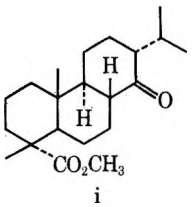
The presence of two ir bands at 3480 and 3360 cm^{-1}, a positive periodate test, and the formation of an acetonide established the presence of a vicinal glycol system whose hydroxyl groups were tertiary and secondary because the nmr spectrum contained only one characteristic low-field singlet at 4.22 ppm. The chemical shift of this signal indicated that it was allylic to a trisubstituted double bond (narrowly split vinyl multiplet at 5.58 ppm). The chemical shift of the C-10 methyl signal at 0.81 ppm was comparable to that found in a number of 8α-hydroxyabietanes[15] and not deshielded as would be expected in a 8β-hydroxyabietane. Oxidation of **8** afforded an α,β-unsaturated α-hydroxy ketone **9** (ir frequencies at 3400 and 1670 cm^{-1}) whose nmr spectrum exhibited a one-proton multiplet at 6.62 ppm typical of protons attached to the β position of an α,β-unsaturated ketone and a methyl signal at 0.67 ppm indicating a shielded C-10 methyl group.

The formation of **8** and **2b** can be rationalized by path b, Scheme II, or perhaps more plausibly by transformation of **2b** *via* lactone interchange into an unstable β-lactone A (path c) which undergoes facile decarboxylative elimination[16] (step d).[17]

The yield of **8** was improved to 60% and the yield of **5** was reduced to below 5% when the pyrolysis of **2b** was carried out in the presence of alumina. On the other hand, addition of catalytic amounts of manganese dioxide to **2b** increased the yield of **5** to 70% and completely suppressed the formation of **8**. In terms of Scheme II, the effect of alumina in promoting formation of **8** could perhaps be attributed to preferential coordination of the Lewis acid with the accessible carbonyl group. This would enhance the electrophilic character of C-21, thus favoring path b or c at the expense of path a. The effect of MnO_2 is more difficult to rationalize. It is possible that formation of a metal complex with the glycol system suppresses nucleophilic attack by the C-13 oxygen on the carbonyl group which is postulated to trigger the conversion of **2b** to **8**. Simultaneously the O–H bonds are weakened and proton transfer to the lactone ether oxygen is encouraged, thus lowering the energy of path a.

In order to shed light on the unusually facile and, we believe, unprecedented decarboxylation of **4a** to **5**, the reaction of **4b** with NaOD–CH_3OD was allowed to proceed for 20 hr. The resultant mixture of products was methylated and separated into **4b** and **5**. Mass spectrometric analysis of **4b** demonstrated the presence of 27% excess **4b**-d_2, 67% **4b**-d_3, 3% **4b**-d_4, and 3% **4b**-d_5.

(9) In **4b** the doublets are found at 0.90 and 0.64, in **5** at 1.00 and 0.67, and in **13** at 0.92 and 0.75 ppm. By comparison, the isopropyl doublets of i,[10] where, even though ring C is a chair, the relative orientation of isopropyl



i

and carbonyl groups reflects approximately the situation expected to prevail in the twist form **4B**, occur at 0.89 and 0.82 ppm.

(10) J. W. Huffmann, T. Kamiya, L. H. Wright, J. J. Schmid, and W. Herz, *J. Org. Chem.*, **31**, 4128 (1966).

(11) That the previously mentioned difference between a 1,3-diaxial H,H and a skew carbomethoxy–isopropyl interaction in chair **4'b** is sufficient to make up the conformational free-energy difference between **4b** and **4'b** of more than 2.5 kcal necessary to account for the strongly preponderant, if not exclusive, presence of **4b** at equilibrium is not easily seen. It is probable that other factors also assist in lowering the conformational energy of **4b** or raising that of **4'b**.

(12) D. S. Noyce, S. K. Brauman, and F. B. Kirby, *J. Amer. Chem. Soc.*, **87**, 4355 (1965).

(13) The formation of **5** during the NaOH–MeOH treatment of **4b** was obviously the result of partial hydrolysis followed by decarboxylation.

(14) For naming and numbering of abietanes, see ref 6 of W. Herz and J. J. Schmid, *J. Org. Chem.*, **34**, 3464 (1969).

(15) W. Herz, R. C. Ligon, H. Kanno, W. H. Schuller, and R. V. Lawrence, *ibid.*, **35**, 3338 (1970).

(16) H. E. Zaugg, *Org. React.*, **8**, 305 (1954).

(17) Retention of the hydroxyl group at C-14 and α orientation of the hydroxyl group at C-8 requires that the path leading from **2b** to **8** not involve cleavage of the C-8–oxygen bond, since otherwise the inevitable 14 → 8 hydride shift[3] leading to a B/C transfusion intervenes.

The position of entry of two of the deuterium atoms was revealed by the nmr spectrum, which showed not only complete disappearance of the H-12 signal (*vide supra*) but collapse of the doublets of the isopropyl group. *Hence H-15 of* **4b** *had been replaced by deuterium* and the third deuterium atom must have entered at C-8.[18] Similarly, analysis of **5** showed the presence of 36% excess **5**-d_3 and 64% **5**-d_4. Again, the nmr spectrum demonstrated *complete substitution of H-15 by deuterium;* by analogy with **4b** it was assumed that the three remaining deuterium atoms had replaced H-8 and H-12. Decarboxylation of **4a** in a $NaOD$–CH_3OD medium or treatment of **5** with $NaOH$–CH_3OD also resulted in substitution of H-15 by deuterium.

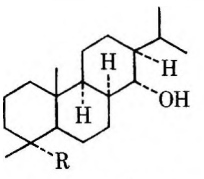
The surprising entry of deuterium into the 15 position of both **4b** and **5** indicated that decarboxylation of **4a** and deuterium exchange in **4b** and **5** involved identical or similar intermediates of a type that permits decarboxylation and quantitative incorporation of deuterium at positions which are not activated in the usual sense. To investigate the possible intervention of homoenolization[19] which affords such intermediates, we decided to study exchange reactions of derivatives of **4b** or **5** which lacked the 14-keto or the 13-hydroxyl group.

Attempts to functionalize the keto group of **4b** for eventual removal by conventional methods or to dehydrate **4b** under mild conditions resulted in recovery of starting material. Reaction of **5** with ethanedithiol took an unexpected course (see Experimental Section), but reduction of **5** with $NaBH_4$ gave a crystalline glycol **10a**. Its nmr spectrum exhibited a one-proton doublet at 3.25 ppm attributable to H-14, whose splitting (J = 10 Hz) clearly indicated its trans diaxial relationship to H-8. As expected, treatment of **10a** with CH_3OD–CH_3ONa and subsequent methylation resulted in recovery of starting material whose nmr and mass spectra showed no incorporation of deuterium.

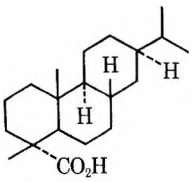
Treatment of **5** with thionyl chloride–pyridine and separation by preparative tlc afforded two α,β-unsaturared ketones, **7** and **11**. The chromophore of **7** was evidenced in the uv (λ_{max} 237 nm), ir (1680 and 1660 cm^{-1}), and nmr spectrum (H-12 triplet at 6.7 ppm, J = 4 Hz, allylic H-15 heptuplet at 2.85 ppm), that of **11** in the ir (cisoid α,β-unsaturated ketone because of the relative intensities of bands at 1680 and 1650 cm^{-1}) and nmr spectrum (two vinyl methyl signals at 1.80 and 1.96 ppm, no methyl doublets or vinyl proton multiplets). The additional observation that **11** was the product of kinetic control and that it was gradually converted to the equilibrium product **7** further supports the equatorial orientation of the hydroxyl group at C-13.

Catalytic hydrogenation (Pd/C) of **7** gave two saturated ketones separable by preparative tlc which had to be C-13 epimers. The less polar ketone, mp 74–76°, was identical with authentic **12** prepared in the course of earlier work,[10,20] a circumstance which clearly established the validity of the conclusions reached earlier with respect to the stereochemistry at C-8 of **4b**, **5**, and **7**. The more polar ketone, mp 128–130°, was therefore the C-13 epimer **13**. Its negative Cotton effect (a = −172), somewhat larger than that of **12**, showed that the octant rule can be applied safely to this system. $NaBH_4$ reduction of **13** gave alcohol **14**, which had an equatorial, hence β-oriented hydroxyl group (H-14 multiplet at 3.38 ppm, $W_{1/2}$ = 15 Hz).[21]

Treatment of **12** or **13** with $NaOCH_3$–CH_3OH gave the same equilibrium mixture containing 90% **12** and 10% **13**; obviously, the stable orientation of H-8 in this system is β. Treatment of **12** with $NaOCH_3$–CH_3OD gave an equilibrium mixture from which deuterated **12** (32% **12**-d_1 and 68% **12**-d_2 by mass spectrometric analysis) was isolated by preparative tlc. The nmr spectrum of the deuterated **12** retained the doublets of the isopropyl group in undiminished intensity. Obviously only H_8 and H_{13} had been exchanged by the usual enolization process and the idea that homoenolization might be responsible for deuterium incorporation only at C-13. The preparation of authentic **13** described in the present communication required revision of the structure assigned to B. Now a third 14-ketone, mp 134–135°, has been prepared[10] by reactions which unambiguously establish its stereochemistry as **17** and has been converted to **12** by treatment with base. Since there are only four possible ketones with a gross structure corresponding to **12** but differing from each other at C-8 and/or C-13, and since three of these (**12**, **13**, and **17**) are known, ketone B must have the stereochemistry represented by **18**. The transformation of **18** to **16** must therefore have been attended by epimerization at C-8 during the ketalization steps, an occurrence whose possibility has already been demonstrated by earlier work[10] in this laboratory.



15a, R = CH_2OH
b, R = CO_2H
c, R = CO_2CH_3



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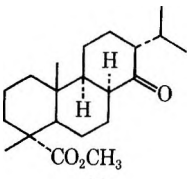

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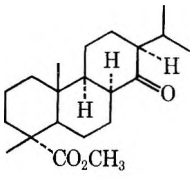


18

Our conclusions on the structure of B were communicated to Professors Huffmann and Burgstahler who have incorporated them in more recently published material and have provided additional evidence for the new structural assignment.[23,24]

(18) This was not obvious from the nmr spectrum, since the H-8 signal of undeuterated **4b** is obscured. Prolongation of reflux time resulted in decrease and eventual disappearance of **4b**-d_2 and **5**-d_3. Simultaneously, the percentage of **4b**-d_3 and **5**-d_4 increased.

(19) A. Nickon and J. L. Lambert, *J. Amer. Chem. Soc.*, **84**, 4606 (1962); **88**, 1905 (1966), and references cited therein. For a recent report of cyclopropanol formation under homoenolization conditions, see P. S. Venkataramani, J. E. Karoglan, and W. Reusch, *ibid.*, **93**, 269 (1971). However, no example of homoenolization-induced decarboxylation has been reported.

(20) A. W. Burgstahler, J. N. Marx, and D. F. Zinkel, *J. Org. Chem.*, **34**, 1550 (1969).

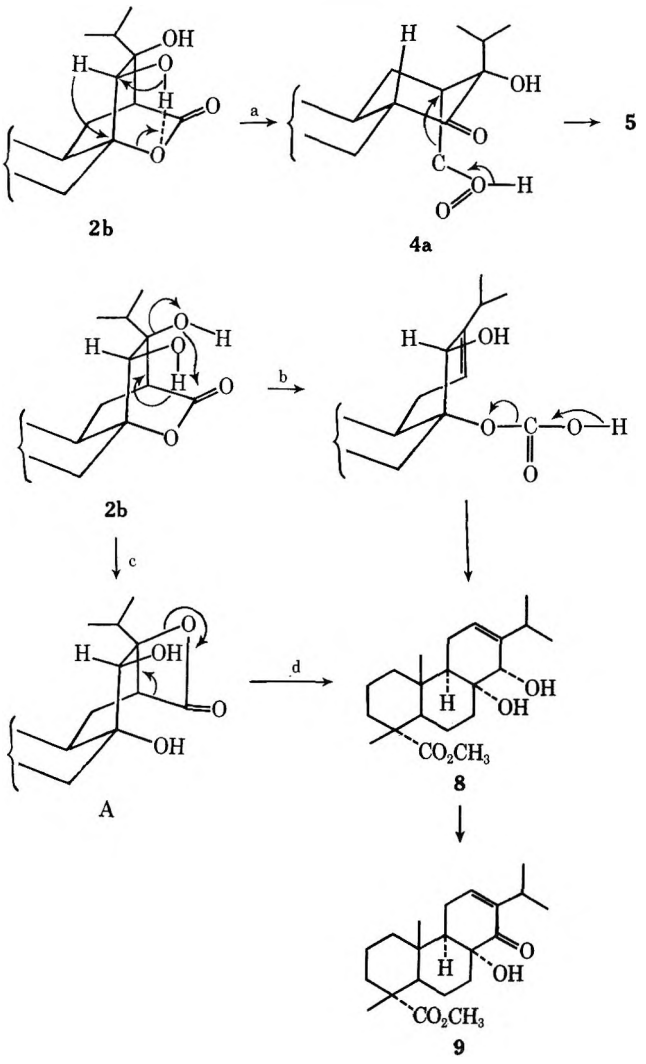
(21) While this work was in progress, Burgstahler and coworkers[20] reported preparation of a ketone B, mp 79–79.5°, for which formula **13** was proposed. Their reaction sequence started with 8(14)-abieten-18-oic acid, hydroboration–oxidation of which gave a diol **15a**. Oxidation of **15a** produced a noncrystalline keto acid methylated to a gummy ester B which was subsequently obtained in crystalline form by following the sequence methyl 8(14)-abieten-18-oate → **15c** → B. B was assigned formula **13** (presumably as the result of epimerization at C-8 but not at C-13 during the oxidation step), the configurational assignment for B being based on the negative ORD curve, the unhindered nature of the carbonyl group, and its conversion to the abietanoic acid **16** *via* the thioketal of B. Huffmann and Alford[22] also prepared A by a similar sequence. Both groups converted B to the ketone **12** by treatment with base, a reaction which they assumed involved epimerization only at C-13. The preparation of authentic **13** described in the present communication required revision of the structure assigned to B. Now a third 14-ketone, mp 134–135°, has been prepared[10] by reactions which unambiguously establish its stereochemistry as **17** and has been converted to **12** by treatment with base. Since there are only four possible ketones with a gross structure corresponding to **12** but differing from each other at C-8 and/or C-13, and since three of these (**12**, **13**, and **17**) are known, ketone B must have the stereochemistry represented by **18**. The transformation of **18** to **16** must therefore have been attended by epimerization at C-8 during the ketalization steps, an occurrence whose possibility has already been demonstrated by earlier work[10] in this laboratory.

(22) J. W. Huffmann and J. Al Alford, Abstracts, Fifth International Symposium on the Chemistry of Natural Products, July 8–13, 1968, p 325.

(23) A. W. Burgstahler, J. N. Marx, and D. F. Zinkel, *J. Org. Chem.*, **34**, 3716 (1969) (correction).

(24) J. W. Huffman, J. A. Alford, and R. R. Sobti, *ibid.*, **35**, 473 (1970).

SCHEME II



poration at C-15 in **4b** and **5** and for decarboxylation of **4b** could be dismissed.

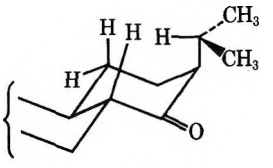
The experiments with **10a**, **12**, and **13** established, however, that both the C-13 hydroxyl and the 14-keto group were essential for the introduction of deuterium at C-12 and C-15 during the decarboxylation of **4a** and the exchange reaction of **5** and that the deuteration at these centers derives from a rearrangement in the course of which both H-12 protons and H-15 become enolic. This requirement is satisfied by invoking an acyloin rearrangement[25,26] which as particularized in Scheme III for **5** (R = H) must be degenerate. In the case of **4a**, whether it be formed from **4b** by pyrolysis or hydrolysis, Scheme III contains intermediates which as β-keto acids are subject to facile decarboxylation and are then in equilibrium with **5**.

To explain the results of the deuterium exchange reaction, it was necessary to assume that the C-8–C-14 and the C-12–C-13 bonds migrate during the course of the reaction but that the overall result which produces no change in structure involves a degenerate acyloin rearrangement which would not have been detected in the absence of a carbomethoxy group at C-12 of **4b**. Thus reversible retrogression of **5** (or **4b**) by migration of the C-12–C-13 bond gives II, which can undergo deuterium exchange at C-15. Reversible ring expansion of II by migration of the C-8–C-14 bond either results in formation of ions III and IV which can undergo deuterium exchange at C-12, or leads to V, the precursor of stereoisomer **21** or **5**. Decarboxylation of **4a** presumably proceeds through an intermediate of type III or IV under basic conditions and probably under pyrolytic conditions as well.

The factors which favor ring expansion and contraction over methyl migration in the D-homoannulation of 17-hydroxy-20-keto steroids[25] (migration of a tertiary in preference to a primary center) are presumably not operative here, so that a direct path from I to III by migration of the isopropyl group is conceivable. However, even then, the return to **4b** or **5** would, because of the introduction of deuterium at C-15, require passage or leakage through ion II. Furthermore ion II (R = H) is required as an intermediate to account for the transformation of **21** to **5** (*vide infra*).

Scheme III suggests that **5** is in equilibrium not only with **20** and **22**, but also with the other three possible isomers **19**, **21**, and **23**, and that **5** represents the most stable isomer. This is reasonable because **19** and **23** are 1-acylcyclopentanols, which are known[25c] to be unstable with respect to the 2-alkyl-2-hydroxycyclohexanol systems represented by **5**, **20**, **21**, and **22**. Isomers **20** and **22**, although more stable than **19** and **23**, are undoubtedly less stable than **5** and **21**, due to the presence of extra interactions between H-7 and the axial substituent of C-14.

That **5** should be more stable than **21** as required by Scheme III seemed initially somewhat puzzling but can be rationalized since in the preferred conformation C[27] the interactions between methyl groups and the



C

axial hydrogens on ring C are minimized and since, due to the 2-alkyl ketone effect,[28] the conformational energy of an α-isopropyl group in cyclohexanones is 0.6 kcal/mol or less.[29,30] Thus even a small amount of assistance from another source can shift the equilibrium in favor

(25) For base-catalyzed rearrangements of open-chain and monocyclic acyloins, see (a) D. B. Sharp and E. L. Miller, *J. Amer. Chem. Soc.*, **74**, 5643 (1952); (b) D. Y. Curtin and S. Leskowitz, *ibid.*, **73**, 2633 (1951); (c) I. Elphimoff-Felkin and A. Skrobek, *Bull. Soc. Chim. Fr.*, 742 (1959). Aspects of the base-catalyzed acyloin rearrangement of 17-hydroxypregnan-20-ones to D-homoandrostane derivatives are reviewed by (d) L. F. Fieser and M. Fieser, "Steroids," Reinhold, New York, N. Y., 1959, p 576; (e) N. L. Wendler in "Molecular Rearrangements," P. de Mayo, Ed., Interscience, New York, N. Y., 1964, p 1099; (f) D. N. Kirk and M. P. Hartshorn, "Steroid Reaction Mechanisms," Elsevier, Amsterdam, 1968, p 294; (g) D. N. Kirk and A. Mudd, *J. Chem. Soc. C*, 2045 (1970).

(26) Homoenolization has been excluded as a mechanism for the degenerate acyloin rearrangement of 1-hydroxynorbornan-2-one: A. Nickon, T. Nishida, and Y. Lin, *J. Amer. Chem. Soc.*, **91**, 6860 (1969). For the rearrangement of 3,3-dimethyl-1-hydroxynorbornanone, see A. Nickon, T. Nishida, J. Frank, and R. Muneyuki, *J. Org. Chem.*, **36**, 1075 (1971).

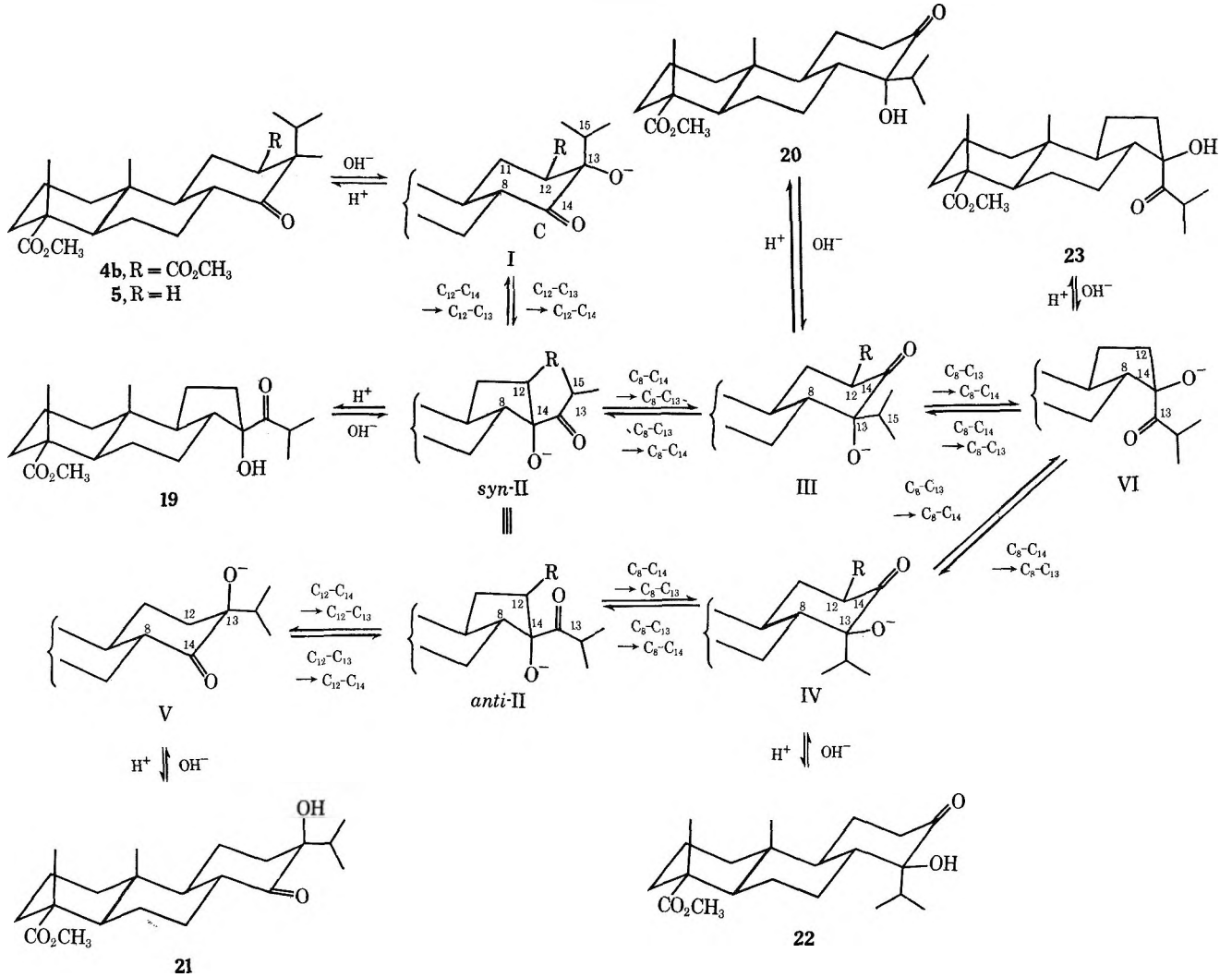
(27) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience, New York, N. Y., 1965, p 458. The chemical shifts of the isopropyl doublets mentioned earlier support this conformation.

(28) Reference 25, p 113.

(29) B. Rickborn, *J. Amer. Chem. Soc.*, **84**, 2414 (1962).

(30) The equilibrium mixture of 2-isopropylcyclohexanone contains 66–67% of the equatorial and 29–34% of the axial conformer: C. Djerassi, P. A. Hart, and C. Beard, *ibid.*, **86**, 85 (1964).

SCHEME III



of an axial isopropyl group.[31] Although the conformational energy of a hydroxyl group in an α-ketol is not known, the presence of such a group may be expected to shift the equilibrium further toward **5**, particularly if, as is apparent from the models, the opportunity for strong intramolecular hydrogen bonding exists in **5**, as was in fact verified by experiment (*vide supra*), and not in **21**.

The likelihood of gaining access to the unstable isomers **19**, **20**, **22**, and **23** by synthesis for the purpose of testing all of the equilibria in Scheme III seemed very dubious. However, the preceding speculations on the relative stability order of **5** and **21**, and therefore the existence of the most important intermediate I, could be placed on a secure footing by successful transformation of **5** into **21**. The diol **10a** gave a gummy mesylate **10b** which was converted to the crystalline epoxide **24b** by refluxing with 5% methanolic sodium hydroxide.[32] Hydrolysis of **24b** gave **24a**, mp 214–216°, which was different from an acid, mp 226–228°, which has been prepared recently[24] by epoxidation of 13-abieten-18-oic acid and to which, on the basis of previous experience that reagent approach to 13-abietenes occurs preferentially from the β side, formula **25** had been tentatively assigned. The unambiguous synthesis of **24a** described here now confirms the conclusions reached by the Clemson workers.

Perchloric acid cleavage of **24b** gave a mixture from which a gummy diol was isolated after preparative tlc. Formation of the anticipated trans-diaxial glycol **26** was confirmed by the nmr spectrum, which displayed a broadened one-proton peak ($W_{1/2}$ = 5 Hz), thus indicating that the relationship of H-14 to H-8 was cis rather than trans. Oxidation of **26** furnished **21**, which could not be induced to crystallize and differed in other important respects from **5**. In line with the earlier discussion, there was no evidence of intramolecular hydrogen bonding. In the nmr spectrum the methyl doublets of **21** were almost superimposed (0.91 and 0.90 ppm) because the equatorial orientation of the isopropyl group removes the methyls from the shielding cone of the ketone function. The amplitude of the negative Cotton effect (a = −117) was considerably lower than that of **5**, perhaps because of the "*anti*-octant" behavior of the now axial hydroxyl group.[8]

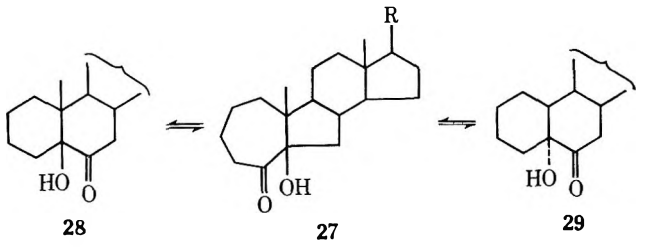
Treatment of **21** with 5% methanolic sodium hydroxide resulted in complete conversion to **5**. Rep-

(31) *Cf.* the situation prevailing in (+)-isomenthone, whose equilibrium mixture consists of 80–88% of the conformer with an axial and 12–20% of the conformer with an equatorial isopropyl group.[29]

(32) Although the stereochemistry of **24b** is without question because of its method of preparation, the half-height width of the H-14 signal (3 Hz) could not be used to confirm this, since models indicate that the H-8–H-14 dihedral angles would be almost the same irrespective of the orientation of the epoxide ring. However, in the β orientation one would expect deshielding of the C-10 methyl signal; this was not observed.

etition of the experiment with MeOD–CH_3ONA produced **5**, whose nmr spectrum showed complete incorporation of deuterium at H-15.[33] This result is in complete agreement with Scheme III.

Attempts were made to monitor the exchange reaction of **5** in an nmr tube in order to detect peaks caused by the presence of the unstable isomers. Such peaks could not be observed; hence it was assumed that the concentration of the isomers was sufficiently small (<5%) to excape detection. This failure parallels the results of Mazur and Nussim,[34] who effected complete rearrangement of the A-homo-B-nor steroid **27** to the cis ketol **28** with 2% methanolic KOH. Treatment of **28** and the trans ketol **29** separately with 10% methanolic KOH gave the same equilibrium mixture containing 92% **28** and 8% **29**. Although **28** and **29** are interconvertible only through **27**, the presence of the latter in the equilibrium mixture could not be detected.



28 **27** **29**

Experimental Section[35]

Methyl 12α-Carbomethoxy-13α-hydroxy-14-oxoabietan-18-oate (4b).—A solution of 25 g of **2b** in 500 ml of methanol saturated with gaseous HCl was allowed to stand overnight. Tlc of the wine red solution indicated disappearance of starting material. After removal of solvent, the residue was diluted with water, filtered, and washed repeatedly with cold water. Recrystallization from methanol–water gave 24.2 g (96%) of **4b** which had mp 139–140°; ir bands at 3480 (–OH), 1740, 1730 (two esters), and 1710 cm^{-1} (ketone); nmr signals at 3.88 (–OH), 3.60 (two methoxyls), 3.34 m, (H-12), 1.18 (C-4 methyl), 0.99 (C-10 methyl), 0.90 d and 0.64 d ppm (J = 6.5 Hz, isopropyl methyls); ORD curve $[\phi]_{298}$ −9280°, $[\phi]_{280}$ ±0°, $[\phi]_{234}$ +11,950°.

Anal. Calcd for $C_{23}H_{36}O_6$: C, 67.62; H, 8.88; O, 23.50. Found: C, 67.66; H, 9.08; O, 23.34.

Stirring of 1 g of **4b** with 10 ml of 2% methanolic sodium hydroxide at room temperature for 2 hr and evaporation of solvent at reduced pressure followed by addition of water and acidification gave 0.9 g of **4a**. Recrystallization from ether–hexane yielded the analytical sample which melted at 193–195°.

Anal. Calcd for $C_{22}H_{34}O_6$: C, 66.98; H, 8.69; O, 24.33. Found: C, 67.17; H, 8.83; O, 24.24.

Solution of **4a** in a methanolic solution of HCl overnight followed by the usual work-up gave a quantitative yield of **4b**.

Attempted Epimerizations of 4b. Isolation of 5. A.—A solution of 5 g of **4b** in 50 ml of 5% methanolic sodium hydroxide was refluxed for 18 hr. The solvent was removed at reduced pressure, water was added, and the mixture was acidified with 2 *N* HCl. The precipitate was washed with cold water, dried, and methylated with diazomethane. Evaporation of solvent gave a solid which contained **4b** and a minor component (tlc). Column chromatography gave 4.2 g of **4b**, identical in all respects with starting material. The minor component **5** had mp 160–161°; ir bands at 3480 (–OH), 1720 (ester), and 1700 cm^{-1} (ketone); nmr signals at 3.84 (–OH), 3.66 (methoxyl), 1.20 (C-4 methyl), 1.00 (C-10 methyl), 1.00 d and 0.67 d ppm (J = 6.5 Hz, isopropyl methyls); ORD curve $[\phi]_{400}$ −437°, $[\phi]_{310}$ −7145°, $[\phi]_{302}$ −8457°, $[\phi]_{286}$ ±0°, $[\phi]_{260}$ +12,250°, $[\phi]_{250}$ +11,370°. The position and shape of the hydroxyl band was not affected when the ir spectrum was run at different concentrations in CCl_4 solution indicating the existence of intramolecular hydrogen bonding.

Anal. Calcd for $C_{21}H_{34}O_4$: C, 71.96; H, 9.78; O, 18.26. Found: C, 71,77; H, 9.92; O, 18.58.

B.—A solution of 1 g of **4b** in 20 ml of 5% NaOD in CH_3OD was refluxed for 18 hr while being protected from atmospheric moisture, worked up as before but acidified with 2 ml of 38% DCl in D_2O prior to addition of water. The precipitate was filtered, washed with water, dried, methylated with diazomethane, and chromatographed. Nmr and mass spectra of the deuterated samples of **4b** and **5** were detailed in the Discussion. Prolongation of the reflux period resulted in an increase in the proportion of **4b**-d_3 and **5**-d_4.

Decarboxylation of 4a.—**4a** (0.5 g) was heated in a nitrogen atmosphere to 280° and held at this temperature for 5 min. Cooling and recrystallization of the product from chloroform–hexane afforded 0.32 g (70%) of **5**.

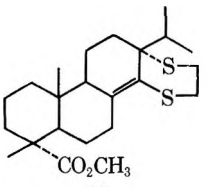
Pyrolysis of 2b. Preparation of 5 and 8. A.—Heating 5 g of **2b** to 280° in the manner described in the previous paragraph followed by chromatography of the crude product over alumina F-20 and elution with benzene afforded a 30% yield of **5** and 10% of a more polar substance **8** which melted at 136° after recrystallization from hexane. It had ir bands at 3480 and 3360 (two –OH) and 1720 cm^{-1} (ester), and nmr signals at 5.58 m ($W_{1/2}$ = 9 Hz, H-12), 4.22 br ($W_{1/2}$ = 6 Hz, H-14), 3.72 (methoxyl), 2.98 (two –OH), 1.18 (C-4 methyl), 1.06 d and 1.05 d (J = 7, isopropyl methyls), and 0.81 ppm (C-10 methyl).

Anal. Calcd for $C_{21}H_{34}O_4$: C, 71.96; H, 9.78; O, 18.26. Found: C, 71.70; H, 9.95; O, 18.41.

B.—An intimate mixture of 5 g of **2b** and 10 g of alumina F-20 was heated in a nitrogen atmosphere at 280° for 10 min. Chromatographic separation of the crude product afforded a 60% yield of **8** and a 5% yield of **5**.

C.—A ground mixture of 2 g of **2b** and 0.2 g of MnO_2 (Baker analyzed) was heated at 280° for 10 min. Chromatographic separation gave 1.3 g (70%) of pure **5**.

A mixture of 1 g of **5**, 2 ml of ethanedithiol, and 0.5 ml of boron trifluoride etherate was left overnight and diluted with methanol. The precipitate was filtered and washed with methanol. Since tlc showed the presence of one main and several minor components, it was purified by preparative tlc. Elution with benzene–acetone (19:1) gave a major noncrystalline but homogeneous fraction which was not the expected thioketal because of the absence of hydroxyl peaks in the ir and nmr spectra and not a dehydration product because the nmr spectrum exhibited no signals characteristic of vinyl protons or vinyl methyl groups, but only the normal methyl doublets of the isopropyl group. The incorporation of ethylenedithiol was shown by the presence of a four-proton peak at 3.16 ppm. This material was tentatively assigned formula **30**. Raney nickel desulfurization furnished a



30

mixture which exhibited neither –OH absorption in the ir nor vinyl proton peaks in the nmr indicating that **30** had been transformed into a mixture of esters of tetrahydroabietic acids.

Methyl 8α-Hydroxy-14-oxoabiet-12-en-18-oate (9).—To a solution of 0.5 g of **5** in 10 ml of acetone, Jones reagent was added with stirring and cooling until the yellow color of the reagent persisted (10 ml). The mixture was poured into water and extracted with ether. The washed and dried ether extracts gave 0.45 g of solid which was recrystallized from hexane–chloroform and then melted at 159.5–160°: ir bands at 3350, 1729, and 1668 cm^{-1}; nmr signals at 6.58 m (H-12), 3.69 (methoxyl), 2.20 (–OH), 1.10 (C-4 methyl), 1.03 d and 1.01 d (J = 6 Hz, isopropyl methyls), and 0.69 ppm (C-10 methyl).

Anal. Calcd for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26; O, 18.36. Found: C, 72.19; H, 9.30; O, 18.50.

(33) Just as in the case of **4b** and **5** itself (footnote 18), the relative proportion of **5**-d_3 and **5**-d_4 depended on the reaction time (mass spectral analysis), although in every run, complete deuteration had taken place at C-15 (nmr analysis). We assume that deuterium exchange at C-8 which involves a sterically unfavorable abstraction and deuteration process is slower than exchange at C-12 and certainly slower than at C-15.

(34) Y. Mazur and M. Nussim, *Tetrahedron Lett.*, 817 (1961).

(35) For details concerning methods, see footnote 52 of ref 17. Mass spectra were run on a Nuclide 12 in medium-resolution mass spectrometer.

Methyl 13α,14β-Dihydroxyabietan-18-oate (10a).—A solution of 5 g of **5** in 60 ml of absolute ethanol containing 1 g of $NaBH_4$ was allowed to stand for 1 hr. Tlc of the mixture showed complete disappearance of starting material. Addition of water precipitated solid **10a** which was recrystallized from methanol (yield quantitative) and had mp 188–190°; $[\alpha]^{27}D$ −15.4° ($CHCl_3$); ir bands at 3580 and 3460 (–OH) and 1720 cm^{-1} (ester); nmr signals at 3.69 (methoxyl), 3.28 d (J = 10 Hz, H-14), 2.24 br (two –OH), 1.19 (C-4 methyl), 1.10 d and 0.90 d (J = 7 Hz, isopropyl methyls), and 0.88 ppm (C-10 methyl).

Anal. Calcd for $C_{21}H_{36}O_4$: C, 71.55; H, 10.29; O, 18.15. Found: C, 71.76; H, 10.28; O, 18.24.

A solution of 0.2 g of **10a** in 5 ml of CH_3OD containing 0.2 g of CH_3ONa was refluxed for 18 hr and worked up as described for **4b** and **5**. Mass spectrometric analysis showed that recovered **10a** (yield quantitative) contained no excess deuterium.

Dehydration of 5. Preparation of 7 and 11.—To a solution of 5 g of **5** in 10 ml of pyridine was added at 0° dropwise 2 ml of thionyl chloride with stirring. The reaction was complete after about 6 hr; tlc showed two spots different from starting material. Dilution with water was followed by extraction with ether. Evaporation of the washed and dried extracts gave 4.5 g of residue. A 1-g portion of this was placed on a preparative tlc plate (20 × 40 cm) and developed with benzene–acetone (49:1). Two additional developments were required to separate the bands, which were separated and extracted with chloroform and chloroform–methanol (19:1). Band 1 gave 0.7 g of gummy **7**, which could be crystallized from hexane at −78° and then melted at 62–63°: ir bands at 1730 (ester), 1680, and 1660 cm^{-1} (α,β-unsaturated ketone); λ_{max} 237 nm (ε 7160); nmr signals at 6.72 t (J = 4Hz, H-12), 3.66 (methoxyl), 2.85 m (H-15), 120 (C-4 methyl), 1.00 d (J = 7 Hz, isopropyl methyls), and 0.98 ppm (C-10 methyl); ORD curve $[\phi]_{350}$ (first reading) −4420°, $[\phi]_{330}$ −4800°, $[\phi]_{300}$ −4060°, $[\phi]_{250}$ −9220°, $[\phi]_{235}$ ±0°, $[\phi]_{218}$ +11,070°, $[\phi]_{209}$ ±0°, $[\phi]_{200}$ −19,550° (last reading).

Anal. Calcd for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70; O, 14.40. Found: C, 75.78; H, 9.35; O, 14.61.

The more polar band on elution with chloroform and chloroform–methanol (19:1) gave 0.3 g of semicrystalline **11**, which was recrystallized from pentane and then melted at 138–140; ir bands at 1730 (ester), 1680, and 1650 cm^{-1} (α,β-unsaturated ketone, two bands of approximately equal intensity); nmr signals at 3.72 (methoxyl), 2.95 and 2.80 (vinyl methyls), 1.21 (C-4 methyl), and 0.96 ppm (C-10 methyl).

Anal. Calcd for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70; O, 14.44. Found: C, 75.99; H, 9.41; O, 14.79.

By following the dehydration reaction with tlc, it was noticed that **11** was formed first and that **7** was formed only after passage of time. When the reaction was complete (*i.e.*, after complete disappearance of starting material) the product consisted of **7** and **11**, but on standing all of the **11** was gradually converted to **7**.

Catalytic Hydrogenation of 7.—A solution of 0.5 g of **7** in 20 ml of absolute ethanol containing 0.1 g of 10% Pd/C was hydrogenated for 24 hr at 40 psi. Filtration and evaporation gave a residue which showed two spots of very similar R_f on tlc (benzene–methanol, 19:1). Preparative tlc gave two compounds. The less polar substance on recrystallization from methanol afforded 0.2 g of **12**, mp 74–76°, identical with authentic **12**.[10] The more polar substance **13** was recrystallized from cyclohexane: mp 128–130°; ir bands at 1720 (ester) and 1700 cm^{-1} (ketone); nmr signals at 3.61 (methoxyl), 1.16 (C-4 methyl), 0.97 (C-10 methyl), 0.92 d and 0.75 d (J = 7 Hz, isopropyl methyls); ORD curve $[\phi]_{319}$ −7770°, $[\phi]_{294}$ ±0°, $[\phi]_{283}$ +9390°.

Anal. Calcd for $C_{21}H_{34}O_3$: C, 75.41; H, 10.25; O, 14.35. Found: C, 75.67; H, 10.34; O, 14.05.

A solution of 0.2 g of **13** in 10 ml of methanol containing 0.1 g of sodium methoxide was refluxed overnight. The usual work-up (which included remethylation with diazomethane) followed by preparative tlc resulted in isolation (prior to recrystallization) of **12** and **13** in the ratio 9:1. The same result was obtained when 0.2 g of **12** was refluxed with $NaOCH_3$–CH_3OH and worked up similarly. When a solution of 0.3 g of **13** in 10 ml of CH_3OD containing 0.1 g of sodium methoxide was refluxed overnight and worked up in the manner described for the exchange reaction of **4b**, 0.3 g of a mixture of deuterated **12** and **13** was obtained. Preparative tlc resulted in separation of **12**, which consisted of 32% excess **12**-d_1 and 68% **12**-d_2 by mass spectrometric analysis. A more prolonged reflux period gave an increase in the proportion of **12**-d_2.

Methyl 12α,13α-Epoxyabietan-18-oate (24b).—A solution of 2 g of **10a** in 6 ml of pyridine was mixed with 1 g of methanesulfonyl chloride at 0°, allowed to stand in the refrigerator for 18 hr, poured into cold water, and extracted with ether. The washed and dried ether extracts were evaporated and the gummy residue of **10b**, which was homogeneous by tlc criteria, was refluxed with 20 ml of 5% methanolic sodium hydroxide for 5 hr. Evaporation at reduced pressure and addition of water gave a 90% yield of solid **24b**, which was recrystallized from methanol: mp 115–116°; ir band at 1720 cm^{-1} (ester); nmr signals at 3.66 (methoxyl), 2.80 br ($W_{1/2}$ = 3 Hz, H-14), 1.15 (C-4 methyl), 0.92 d and 0.91 d (J = 6.5 Hz, isopropyl methyls), and 0.80 ppm (C-10 methyl).

Anal. Calcd for $C_{21}H_{34}O_3$: C, 75.41; H, 10.25; 0, 14.35. Found: C, 75.22; H, 10.25; O, 14.70.

Hydrolysis of 0.15 g of **24b** with 15 ml of 5% methanolic sodium hydroxide for 18 hr gave a quantitative yield of **24a**, which was recrystallized from acetone–hexane and melted at 214–216°: $[\alpha]^{27}D$ +8.6° ($CHCl_3$); nmr signals at 2.81 br (H-14), 1.15 (C-4 methyl), 0.91 d and 0.90 d (J = 6.5Hz, isopropyl methyls), and 0.80 ppm (C-10 methyls).

A pure sample of the acid **25**, mp 226–228°, $[\alpha]$ +11°, was no longer available, but the mixture melting point of **24a** with a sample of mp 213–215° supplied by Professor Huffmann was depressed to below 200° and their spectra (KBr pellets) were different.

Anal. Calcd for $C_{20}H_{32}O_3$: C, 74.96; H, 10.06; O, 14.98. Found: C, 74.97; H, 9.74; O, 15.02.

Methyl 13β,14α-Dihydroxyabietan-18-oate (26).—A solution of 1 g of **24b** in 20 ml of tetrahydrofuran containing 2–3 drops of 87% perchloric acid was stirred at room temperature for 1 hr. Tlc showed a mixture with one major spot (40%). The usual work-up followed by preparative tlc gave 0.3 g of a homogeneous gum which had ir bands at 3505, 3480 (hydroxyl groups), and 1710 cm^{-1} (ester); nmr signals at 3.70 (methoxyl), 3.48 br ($W_{1/2}$ = 5 Hz, H-14), 1.20 (C-4 methyl), 0.91 d and 0.90 d (J = 7 Hz, isopropyl methyls), and 0.90 (C-10 methyl).

Methyl 13β-Hydroxy-14-oxoabietan-14-oate (21).—Jones reagent (2 ml) was added to a solution of 0.5 g of **26** in 10 ml of acetone with stirring at ice bath temperature. The reaction was quenched with water after 20 min and extracted with ether. The washed and dried ether layer was removed. The gummy residue (**21**), wt 0.5 g, was purified by chromatography, but could not be induced to solidify. The substance displayed ir bands at 3480 (intermolecularly bonded –OH, displaced to 3580 cm^{-1} in dilute CCl_4), 1730 (ester), and 1715 cm^{-1} (ketone), and nmr peaks at 3.70 (methoxyl), 1.20 (C-4 methyl), 1.00 (C-10 methyl), 0.91 d and 0.90 d (J = 7 Hz, isopropyl methyls); ORD curve $[\phi]_{326}$ −5675°, $[\phi]_{304}$ ±0°, $[\phi]_{280}$ +6040°.

A solution of 0.2 g of **21** in 10 ml of 5% methanolic sodium hydroxide was refluxed overnight. The reaction was worked up in the usual way (this included remethylation with diazomethane) and afforded 0.18 g of recrystallized **5**, mp 160–161°. The reaction was repeated with $NaOCH_3$–CH_3OD and quenched after 2 hr by the addition of water before it was complete. Tlc indicated the presence of a mixture of **21** and **5**. Separation by column chromatography gave pure **5**, whose nmr spectrum indicated that H-15 had been completely replaced by deuterium. Mass spectrometric analysis indicated the presence only of **5**-d_3 and **5**-d_4.

Registry No.—**4a**, 32111-48-1; **4b**, 32111-49-2; **5**, 32111-50-5; **7**, 32111-51-6; **8**, 32111-52-7; **9**, 32111-53-8; **10a**, 32111-54-9; **11**, 32111-55-0; **13**, 19426-98-3; **21**, 32111-57-2; **24a**, 32207-39-9; **24b**, 32111-58-3; **25**, 22565-87-3; **26**, 32111-60-7.

Aziridines. XIX. Substituent Effects in the Pyrolytic Isomerization of 1-Aroyl-2,2-dimethylaziridines[1]

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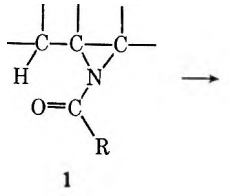
Received June 14, 1971

In a kinetic study of the pyrolytic rearrangement of seven substituted 1-benzoyl-2,2-dimethylaziridines at 79.2°, it was found that the isomeric *N*-(β-methallyl)benzamides are formed in a first-order reaction. The Hammett plot of the rate constants is linear with $\rho = +1.19$. These results provide further support for the conclusion that the rearrangement occurs *via* a transition state with charge separation in the rate-determining step.

The thermal isomerization of *N*-acyl- or aroylaziridines **1** to the isomeric *N*-allylcarboxamides **3** was first reported from our laboratory in 1956 and has been the subject of extensive investigation since that time.[2] These studies have provided support for the view that the reaction is a stereospecific cis elimination involving the transition state **2**. This paper is concerned with a study of the substituent effect in the aroyl group R, which further clarifies the nature of this transition state.



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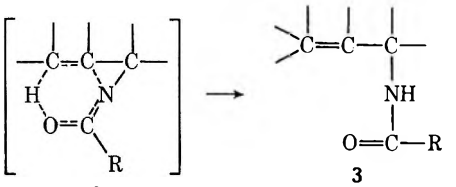
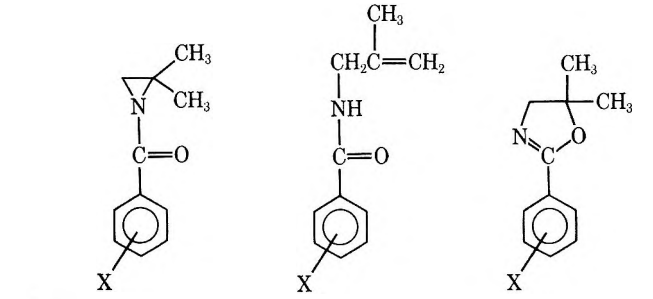


2 **3**

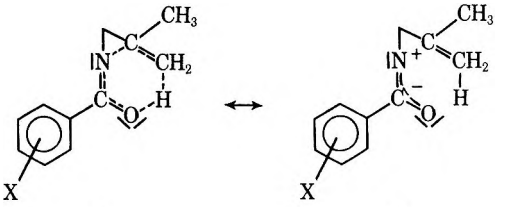
In an earlier publication,[3] it was reported that the thermal isomerization of 1-(*p*-nitrobenzoyl)-2,2-dimethylaziridine (**4a**) to *N*-(β-methallyl)-*p*-nitrobenzamide (**5a**) in diglyme is a first-order reaction with a large negative entropy of activation, which is also in agreement with the proposed mechanism. We have now extended the kinetic study to the six additional benzoyl derivatives **4b–g**. In diglyme at 79.2°, each of these *N*-acylaziridines formed the isomeric amide **5a–g** according to first-order kinetics, with rate constants summarized in Table I. The Hammett plot[4] for these data was found to be linear with no deviations and $\rho = +1.19$ as shown in Figure 1.

The sign and magnitude of the ρ value indicates that the rate-determining step in the unimolecular reaction is the formation of a polarized transition state in which the negative charge is stabilized by the electron-attracting substituents in the phenyl ring. In terms of

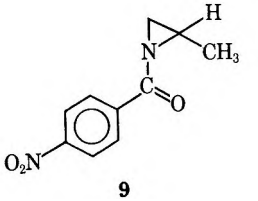


Substituent X			
p-NO_2	**4a**	**5a**	**6a**
m-NO_2	**b**	**b**	
p-CN	**c**	**c**	
m-Br	**d**	**d**	
p-Br	**e**	**e**	
H	**f**	**f**	
p-CH_3	**g**	**g**	**g**

conventional resonance theory, **8** may be regarded as an important contributing form to the resonance hybrid **7**.



7 **8**



9

We also observed that, whereas 1-(*p*-nitrobenzoyl)-2,2-dimethylaziridine (**4a**) underwent isomerization in nitrobenzene with a half-life of about 5 hr at 82°, the homologous monomethyl compound **9** did not rearrange under the same conditions even after 140 hr. This provides further evidence for the participation of contributing structure **8**, in which the positive charge is on a tertiary carbon atom, rather than on a secondary carbon atom as it would be in the analogous transition state from compound **9**.

It is well known that the rate of a reaction increases with the dielectric constant of the medium if the transition state is more polar than the reactants or if the products are ions. Therefore we measured the rate of the isomerization of 1-(*p*-nitrobenzoyl)-2,2-dimethyl-

(1) Abstracted from the Ph.D. Thesis of C. H. Chang, submitted to Illinois Institute of Technology in 1969.

(2) I. J. Burnstein, P. E. Fanta, and B. S. Green, *J. Org. Chem.*, **35**, 4084 (1970), and earlier papers summarized in O. C. Dermer and G. E. Ham, "Ethylenimine and Other Aziridines," Academic Press, New York, N. Y., 1969, p 280.

(3) P. E. Fanta and M. K. Kathan, *J. Heterocycl. Chem.*, **1**, 293 (1964).

(4) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Holt, Rinehart and Winston, New York, N. Y., 1959, p 220.

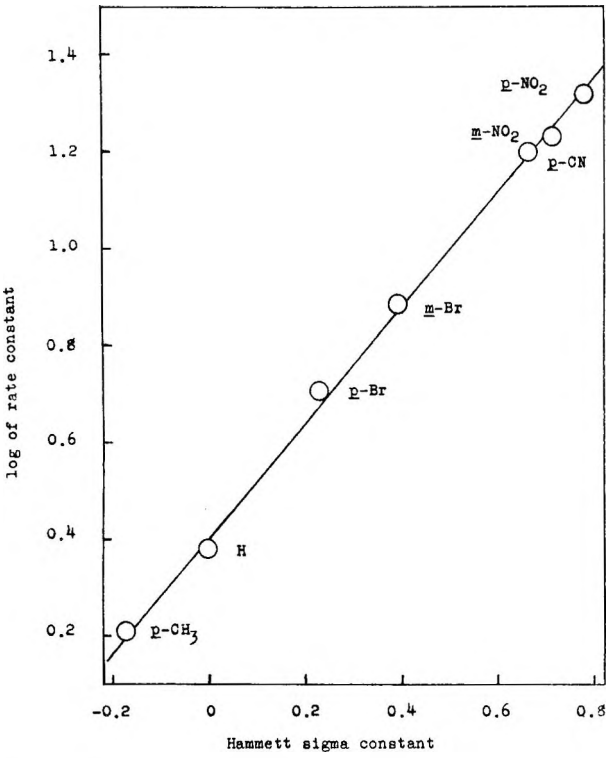


Figure 1.—Hammett plot for the formation of substituted *N*-(β-methallyl)benzamides in diglyme at 79.2°.

TABLE I

RATE CONSTANTS FOR THE FORMATION OF SUBSTITUTED *N*-(β-METHALLYL)BENZAMIDES IN DIGLYME AT 79.2°

Substituent	10^5k, sec^{-1}	Av 10^5k, sec^{-1}
p-NO_2	21.7 ± 0.5	21.3 ± 0.5
	21.6 ± 0.4	
	20.7 ± 0.6	
m-NO_2	18.4 ± 0.4	17.8 ± 0.3
	17.8 ± 0.1	
	17.3 ± 0.3	
p-CN	15.9 ± 0.2	16.1 ± 0.2
	16.1 ± 0.2	
	16.4 ± 0.2	
m-Br	7.52 ± 0.08	7.57 ± 0.10
	7.45 ± 0.15	
	7.75 ± 0.08	
p-Br	5.15 ± 0.13	5.17 ± 0.13
	5.18 ± 0.10	
	5.19 ± 0.16	
H	2.47 ± 0.05	2.43 ± 0.04
	2.28 ± 0.03	
	2.53 ± 0.03	
p-CH_3	1.61 ± 0.02	1.63 ± 0.03
	1.63 ± 0.03	
	1.64 ± 0.02	

aziridine (**4a**) in various solvents of different dielectric constant as summarized in Table II. The small difference in reaction rates suggests that the transition state **7** is not much more polarized than the ground state or that it is poorly solvated.

The effect of variation of temperature on the rate of isomerization of 1-(*p*-nitrobenzoyl)-2,2-dimethylaziridine in both nitrobenzene and chlorobenzene was measured as shown in Table III. These data gave a linear Arrhenius plot and were used for the calculation of the activation parameters, $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$, which are included in Table III. The large negative value for the

TABLE II

RATE CONSTANTS FOR THE DISAPPEARANCE OF 1-(*p*-NITROBENZOYL)-2,2-DIMETHYLAZIRIDINE IN VARIOUS SOLVENTS AT 145°

Solvent	Dielectric constant (25°)	10^5k, sec^{-1}
Nitrobenzene	34.82	6.65 ± 0.16
o-Dichlorobenzene	9.93	5.80 ± 0.21
Chlorobenzene	5.62	5.10 ± 0.04
Bromobenzene	5.40	5.09 ± 0.04

TABLE III

RATE CONSTANTS AND REACTION PARAMETERS FOR THE DISAPPEARANCE OF 1-(*p*-NITROBENZOYL)-2,2-DIMETHYLAZIRIDINE IN NITROBENZENE AND CHLOROBENZENE

Temp, °C	10^5k, sec^{-1}	$\Delta H^{\ddagger}$, kcal/mol	$-\Delta S^{\ddagger}$, eu
	In Nitrobenzene		
82.0	3.97 ± 0.04		
110.4	50.6 ± 0.4		
		23.3	14
132.0	268 ± 4		
145.0	665 ± 16		
	In Chlorobenzene		
82.0	3.37 ± 0.04		
110.4	39.4 ± 0.6		
		22.9	15
132.0	217 ± 2		
145.0	510 ± 4		

entropy of activation, $\Delta S^{\ddagger}$, is consistent with the formation of a cyclic transition state **2**.

By careful examination of the nmr spectrum of the reaction mixture from the pyrolysis of 1-(*p*-nitrobenzoyl)-2,2-dimethylaziridine in nitrobenzene, it was found that the formation of unsaturated amide is accompanied by a small amount of the isomeric oxazoline (**6a**), representing about 3% of the product at 82° and 2% at 145°. This relatively small side reaction is not sufficient to affect the conclusions we have thus far drawn about the mechanism of isomerization.

On the other hand, we found that the isomerization product from the pyrolysis of the *p*-toluyl derivative **4g** in nitrobenzene contained a significantly larger fraction of oxazoline: about 12.8% at 145° and 32.8% at 82°. At 82° in nitrobenzene, 1-(*p*-toluyl)-2,2-dimethylaziridine isomerizes by parallel first-order reactions to give a ratio of unsaturated amide **5g** and oxazoline **6g** which is time independent, as shown by the data in Table IV.

Latvian workers had previously observed an analogous qualitative substituent effect in the isomerization of an aroylaziridine to an oxazoline. On heating at 110° for 2 hr, 1-furoylaziridine gave a 33% yield of the oxazoline, while the 5-nitrofuroyl derivative gave no reaction.[5] This observation, as well as our data, shows that in contrast to the substituent effect found for the isomerization of the acylaziridine to the unsaturated amide, the isomerization to oxazoline is *hindered* by an electron-attracting group in the aroyl moiety.

Such a result can be rationalized by a mechanism in which the rate-determining step is the formation of a transition state represented by the hybrid **10**, with contributing forms **11**, **12**, and **13**. Obviously, contributing form **11** will be destabilized when X is an electron-

(5) M. Lidaks and S. Hillers, *Latv. PSR Zinat. Akad. Vestis, Kim. Ser.*, **2**, 211 (1961); *Chem. Abstr.*, **58**, 4530 (1963), and private conversation.

TABLE IV

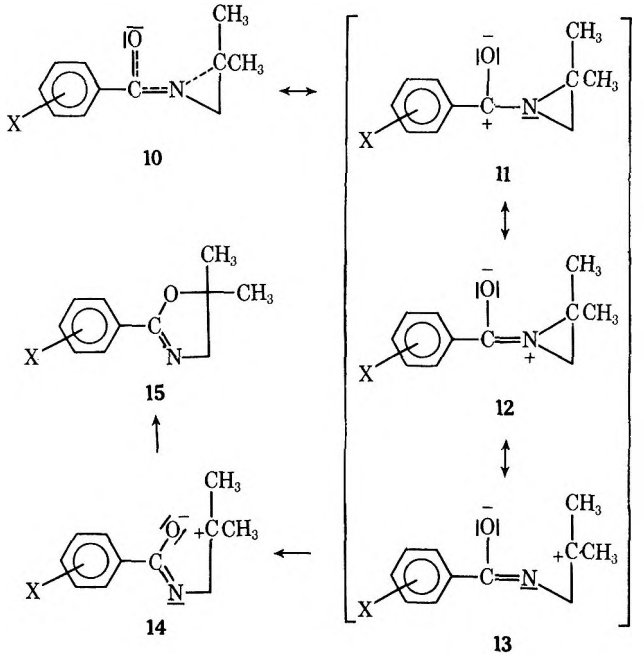
DATA FOR THE PYROLYTIC ISOMERIZATION OF 1-(*p*-TOLUYL)-2,2-DIMETHYLAZIRIDINE IN NITROBENZENE AT 82°

Time, hr	A_t,[a] %	B_t,[b] %	C_t,[c] %	B_t/C_t (= k_1/k_2)[d]
0	100	0	0	
12	85.52	9.80	4.68	2.09
24	73.17	17.68	9.15	1.93
40	56.84	28.40	14.76	1.92
54	45.15	37.00	17.85	2.07
82	28.66	47.10	23.83	1.98
117.5	16.12	56.15	27.24	2.06
135	11.89	58.62	29.01	2.02
∞	0	67.19	32.81	2.05

[a] The percentage of 1-(*p*-toluyl)-2,2-dimethylaziridine in the reaction mixture at time *t*. [b] The percentage of *N*-(β-methallyl)-*p*-toluamide in the reaction mixture at time *t*. [c] The percentage of 2-(*p*-toluyl)-5,5-dimethyl-2-oxazoline in the reaction mixture at time *t*. [d] The ratio of the rate constants for the formation of amide and oxazoline.

attracting substituent, and **13** will be destabilized in the homologous monomethylaziridine. In this mechanism, oxazoline formation is completed by the "unfolding" of **10** to the zwitterion **14**, which then cyclizes to the oxazoline **15** in a fast step.

Interestingly, the nmr chemical shifts of both the methyl and the methylene protons of the aroylaziridines **4a–g** were found to have a linear variation with the Hammett substituent constant σ, as summarized in Figure 2.



Experimental Section

Diglyme was refluxed over calcium hydride and then distilled in the presence of lithium aluminum hydride *in vacuo* prior to use. *p*-Nitrobenzoyl chloride was recrystallized from low-boiling petroleum ether. Microanalyses were carried out by Micro-Tech Laboratories, Inc., Skokie, Ill., and M-H-W Laboratories, Garden City, Mich.

General Procedure for the Preparation of 1-Aroyl-2,2-dimethylaziridines 4a–g.—To a solution of 7.1 g (0.10 mol) of 2,2-dimethylaziridine and 12.1 g (0.12 mol) of triethylamine in 200 ml of dry benzene was added dropwise with stirring a solution of 0.10 mol of substituted benzoyl chloride in 200 ml of dry benzene over a period of 1 hr at *ca.* 5°. The mixture was stirred at *ca.* 5°

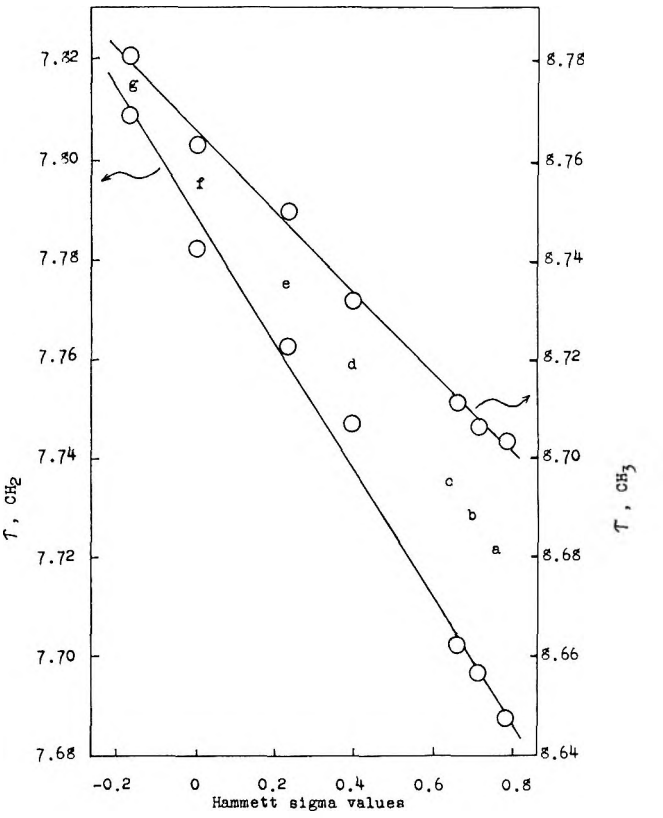


Figure 2.—Correlation of chemical shifts with the substituent constants for substituted 1-benzoyl-2,2-dimethylaziridines **4a–g** (CCl_4, 15% w/v).

for an additional 4 hr and then allowed to warm to room temperature. The triethylamine hydrochloride was removed by filtration and solvent was evaporated *in vacuo* with a rotary evaporator leaving a crude product in 96–98% yield, which was chromatographed on a column containing 15 g of Woelm neutral alumina (grade I). Rapid elution with hexane gave, after evaporation of the solvent, 1-aroyl-2,2-dimethylaziridine. Solid products were recrystallized quickly from low-boiling petroleum ether. Liquid products were chromatographed again on another 10 g of Woelm neutral alumina; the middle fraction from elution with low-boiling petroleum ether was used. Yields of pure products were *ca.* 80%. Physical and analytical data are summarized in Table V.

TABLE V

DATA FOR 1-AROYL-2,2-DIMETHYLAZIRIDINES **4a–g**[a]

Substituent	n^{25}D or mp, °C
p-NO_2	69–70[b]
m-NO_2	58.5–59.5
p-CN	63–64
m-Br	1.5514
p-Br	36.5–37.5
H	1.5328
p-CH_3	40.5–41.5

[a] Satisfactory analytical values (±0.3% for C and H) were reported for all new compounds: Ed. [b] Lit.[6] 78°.

Isolation of Substituted *N*-(2-Hydroxy-2-methylpropyl)benzamides.—Further elution with 4:1 benzene–methanol of each chromatographic column used for the purification of a substituted 1-benzoyl-2,2-dimethylaziridine gave a small yield of the corresponding hydrolysis product, a substituted *N*-(2-hydroxy-2-methylpropyl)benzamide, which was purified by recrystallization from benzene. Data for these derivatives are summarized in Table VI.

2-(*p*-Nitrophenyl)-5,5-dimethyl-2-oxazoline.—An authentic sample was prepared as previously described, mp 144–146° (lit.[6] 146–147.5°).

(6) H. W. Heine, M. E. Fetter, and E. M. Nicholson, *J. Amer. Chem. Soc.*, **81**, 2202 (1959).

TABLE VI

DATA FOR SUBSTITUTED *N*-(2-HYDROXY-2-METHYLPROPYL)BENZAMIDES[a]

Substituent	Registry no.	Mp, °C	Infrared bands (KBr), cm⁻¹ νOH	νNH	νCO
p-NO_2	32158-96-6	139–140	3311	3222	1672
m-NO_2	6332-97-4	129.5–130.5	3312	3233	1672
p-CN	32158-98-8	116–117	3315	3242	1671
m-Br	32158-99-9	96.5–97	3320	3240	1672
p-Br	32159-00-5	139–140	3364	3250	1671
H		105–106	3378	3255	1672
p-CH_3	32159-01-6	133.5–134.5	3398	3264	1674

[a] Satisfactory analytical values (±0.3% for C and H) were reported for all new compounds: Ed.

2-(*p*-Toluyl)-5,5-dimethyl-2-oxazoline.—An authentic sample was prepared in 81% yield by treatment of 1-(*p*-toluyl)-2,2-dimethylaziridine with anhydrous aluminum chloride in refluxing hexane, mp 47–48° after sublimation.

Anal. Calcd for $C_{12}H_{15}NO$: C, 76.11; H, 8.07. Found: C, 76.32; H, 8.25.

1-(*p*-Nitrobenzoyl)-2-methylaziridine was prepared by treatment of 2-methylaziridine and triethylamine in benzene with *p*-nitrobenzoyl chloride. A sample purified by sublimation had mp 78.5–79.5°. The nmr spectrum (in $CDCl_3$) showed multiplets in the following regions: τ 8.62–8.53 (3 H, CH_3), 8.80–8.74 (1 H, CH), 7.46–7.28 (2 H, CH_2), and 1.98–1.58 (4 H, aromatic protons).

Anal. Calcd for $C_{10}H_{10}N_2O_3$: C, 58.25; H, 4.89. Found: C, 58.52; H, 4.90.

Preparation of Substituted *N*-(β-Methallyl)benzamides 5a–g.—A solution of 3.0 g of the substituted 1-benzoyl-2,2-dimethylaziridine in 50 ml of dry xylene was refluxed for 3 hr. After removal of the solvent, the solid residue was recrystallized twice from benzene–hexane. Each compound discharged the purple color of a solution of potassium permanganate in aqueous methanol and had the expected spectral characteristics: an NH band in the infrared at 3235–3280 cm^{-1} and nmr bands ($CDCl_3$) at τ 8.21–8.26 (m, 3 H), 5.96–6.06 (d, J = 6 Hz, 2 H), and 5.10–5.17 (m, 2 H). The nmr NH band was broad and its location was concentration dependent. Other data are summarized in Table VII.

Kinetic Measurements. Infrared Method.—The kinetic values for the formation of the *N*-(β-methallyl)benzamides (data in Table I) were obtained by measuring the change in the NH band in the infrared spectrum near 3347 cm^{-1}, as described in a previous publication.[3] To prevent absorption of atmospheric moisture, the samples in diglyme were prepared and the ampoules were filled in a dry nitrogen atmosphere in a glove box. An initial concentration of 0.200 *M* aroylaziridine was used, and spectra were measured on the Perkin-Elmer Model 257 spectrophotometer, using 0.2-mm NaCl cells.

TABLE VII

DATA FOR SUBSTITUTED *N*-(β-METHALLYL)BENZAMIDES

Substituent	Molecular formula	Mp, °C	Calcd, % C	H	Found, % C	H
p-NO_2	$C_{11}H_{12}N_2O_3$	127–128[a]				
m-NO_2	$C_{11}H_{12}N_2O_3$	94.0–95.5	59.99	5.49	59.84	5.50
p-CN	$C_{12}H_{12}N_2O$	119–120	72.00	6.05	72.52	6.11
m-Br	$C_{11}H_{12}BrNO$	93–94	51.99	4.76	52.09	4.55
p-Br	$C_{11}H_{12}BrNO$	97–98	51.99	4.76	52.14	4.61
H	$C_{11}H_{13}NO$	69–70[b]				
p-CH_3	$C_{12}H_{15}NO$	77–77.5	76.11	8.07	76.25	8.28

[a] Lit.[8] mp 126–127.5°. [b] Mp 69.5–70.5°: J. C. Sheehan and G. D. Laubach, *J. Amer. Chem. Soc.*, **73**, 4376 (1951).

Nmr Method.—The data shown in Tables II–IV were obtained from integration curves of nmr spectra obtained on the Varian A-60 spectrometer. Solutions with a concentration of 10% w/v of aroylaziridine were prepared and handled in a dry nitrogen atmosphere. Only one sealed nmr tube was prepared for each kinetic run. The tube was placed in a thermostated bath and removed at intervals and quenched in an ice bath for determination of the spectrum. It was then returned to the bath for further suitable intervals, until the infinity point at 10 half-lives was reached.

The kinetics of the isomerization of 1-(*p*-nitrobenzoyl)-2,2-dimethylaziridine was followed by measuring the disappearance of the methylene proton band in **4a** and the appearance of the methyl proton bands of **5a** and **6a**. Each integration was run three to five times, and a mean value was calculated. The integration value of the methylene peak of **4a** was tripled and the methyl peak of **5a** was doubled to convert all values to the same scale.

Similarly, the kinetics of the rearrangement of 1-(*p*-toluyl)-2,2-dimethylaziridine in nitrobenzene were followed by measuring the disappearance of the methyl peak in the aroylaziridine (τ 8.75), the appearance of the methyl peak in the unsaturated amide (τ 8.19), and the appearance of the methyl peak in the oxazoline (τ 8.53).

Registry No.—**4a**, 781-86-2; **4b**, 32044-15-8; **4c**, 32044-16-9; **4d**, 32158-84-2; **4e**, 32158-85-3; **4f**, 21384-58-7; **4g**, 32158-87-5; **5a**, 782-83-2; **5b**, 32158-89-7; **5c**, 32158-90-0; **5d**, 32158-91-1; **5e**, 32158-92-2; **5f**, 709-25-1; **5g**, 32158-94-4; **6g**, 32136-34-8; **9**, 21384-47-4.

Nuclear Magnetic Resonance Spectra and Nitrogen Inversion in 1-Alkyl-2-aryl-3-carboaziridines

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Received April 22, 1971

The proton magnetic resonance spectra of several *cis*- and *trans*-1-alkyl-2-aryl-3-benzoylaziridines and *cis*- and *trans*-methyl-1-alkyl-2-aryl-3-aziridine carboxylates were studied over a temperature range of 70 to −40°. The spectra of the cis aziridines show slight temperature dependence while the corresponding trans isomers exhibit major changes in the same temperature range. The results are rationalized in terms of the nitrogen inversion process. Evidence is presented which indicates that the trans isomers exist in a preferred conformation with the *N*-alkyl group syn to the carbonyl. The chemical shifts of the ring protons are rationalized in terms of the anisotropies of the C–N bonds, C–C bonds, and the van der Waals dispersion effects.

Since the first study of the nitrogen inversion process of 1-alkylaziridines utilizing variable-temperature pmr by Bottini and Roberts,[3] the subject has been of intense interest to several investigators.[4] This fact, coupled with our continued interest in aziridine ketones[5] and more recently methyl aziridinecarboxylates,[6] has led us to a detailed pmr study of 1-alkyl-2-aryl-3-benzoylaziridines and 1-alkyl-2-aryl-3-aziridinecarboxylates. Previous reports of the pmr spectra of the cis and trans forms of 1-alkyl-2-aryl-3-aroylaziridines[7] and 1-alkyl-2,-3-dibenzoylaziridines[8] have dealt primarily with chemical shifts, solvent-induced chemical shift differences, and, where appropriate, the spin–spin coupling constants of the aziridine ring protons. When the ring protons are nonequivalent, the vicinal proton coupling constants J_{cis} and J_{trans} lie in the ranges 6.5–7.5 and 2.0–3.5 Hz, respectively. The same reports[7,8] indicated that no additional multiplicity was observed in the ring proton spectra of the aziridine ketones, presumably because the spectra were determined at temperatures where the inversion process was too rapid.

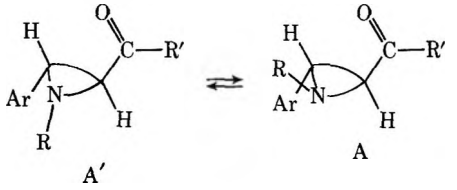
The pmr spectra of these aziridines would be expected to exhibit an AX or AB pattern for the ring protons, C_2 H and C_3 H, if the inversion process is fast relative to the nmr time scale.

By examination of the possible conformations of the trans aziridines (Scheme I), one can see that if the rate of inversion is slowed sufficiently it may be possible to observe A and A′. The ring protons in A would be expected to exhibit an AX or AB pattern and similarly the ring protons in conformer A′ should exhibit an AX or AB pattern. Hence there is a possibility of observing as many as eight lines for the ring protons if the rate of inversion is sufficiently slowed. One will also note that the *N*-alkyl groups of the two conformers may be in different magnetic environments and hence two separate signals for these groups are possible. The greatest effect would be expected for those protons bonded to the carbon atom α to the nitrogen of the *N*-alkyl group. In addition the relative populations of conformers A and A′ may be different.

If the same rationale is applied to the cis aziridines (Scheme II), similar conclusions result.

SCHEME I

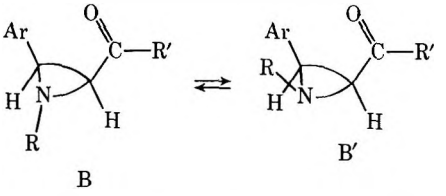
POSSIBLE CONFORMATIONS OF *trans*-1-ALKYL-2-ARYL-3-CARBOAZIRIDINES



R = alkyl; R′ = Ph, OCH_3; Ar = Ph, *p*-$C_6H_5C_6H_4$

SCHEME II

POSSIBLE CONFORMATIONS OF *cis*-1-ALKYL-2-ARYL-3-CARBOAZIRIDINES



R = alkyl; R′ = Ph, OCH_3; Ar = Ph, *p*-$C_6H_5C_6H_4$

We now wish to report the synthesis of several new cis–trans pairs of 1-alkyl-2-aryl-3-aroylaziridines and methyl 1-alkyl-2-aryl-3-aziridinecarboxylates and, also, to report the salient features of the pmr spectra of these and other aziridine ketones and esters. These new data, when examined in light of previous pmr studies of the nitrogen inversion process in aziridines, indicate that the *N*-alkyl substituent in several of the aziridines in question occupies a preferred conformation with respect to the ring carbon substituents.

Results and Discussion

Preparation of Materials.—The previously described methods of Cromwell[9] and Southwick[10] were successfully applied to the synthesis of the 1-alkyl-2-aryl-3-aroylaziridines employed in this study. The cis and trans forms of the methyl 1-alkyl-2-aryl-3-aziridine carboxylates were produced upon treatment of a ben-

(1) Petroleum Research Foundation Fellow, 1968–1969.

(2) To whom inquiries should be addressed.

(3) A. T. Bottini and J. D. Roberts, *J. Amer. Chem. Soc.*, **80**, 5203 (1958).

(4) More recently, (a) J. D. Roberts, *et al.*, *ibid.*, **91**, 642 (1969); (b) K. Mislow, *et al.*, *ibid.*, **92**, 4050 (1970).

(5) For preceding paper in this series see D. K. Wall, J. L. Imbach, A. E. Pohland, R. C. Badger, and N. H. Cromwell, *J. Heterocycl. Chem.*, **5**, 77 (1968).

(6) (a) P. B. Woller and N. H. Cromwell, *ibid.*, **5**, 579 (1968); (b) *J. Org. Chem.*, **35**, 888 (1970).

(7) A. E. Pohland, R. C. Badger, and N. H. Cromwell, *Tetrahedron Lett.*, 4369 (1965).

(8) A. B. Turner, H. W. Heine, J. Irving, and J. B. Bush, *J. Amer. Chem. Soc.*, **87**, 1050 (1965).

(9) N. H. Cromwell, *et al.*, *ibid.*, **73**, 1044 (1951).

(10) P. L. Southwick and W. L. Walsh, *ibid.*, **77**, 405 (1955).

zene or methanol solution of methyl α-bromo-*p*-phenylcinnamate with a 15-fold excess of the primary amine of choice at room temperature for 24–28 hr.[6]

The infrared and ultraviolet spectra of the aziridine ketones and esters are in accord with spectral data of analogous aziridines.[6b,11]

Proton Magnetic Resonance Spectra at 37°.—The ring proton spectra of the cis and trans forms of methyl 1-alkyl-2-aryl-3-aziridinecarboxylates show the same general characteristics as reported for the analogous 1-alkyl-2-aryl-3-aroylaziridines.[7] Thus, the ring protons of the cis isomer appear at higher field than those of the corresponding trans forms. In the trans forms in which the carbonyl group is in the cisoid conformation,[11] both C_2 H and C_3 H are strongly deshielded by the anisotropy of the C_2 phenyl substituent and the carbonyl moiety. Replacement of the phenyl substituent by a methyl substituent in the ketone series results in C_2 H being shifted to higher fields. In 1-cyclohexyl-2-benzoylaziridine, that proton at C_3 which has a cis stereochemical relationship with respect to the aroyl group is strongly deshielded relative to the remaining proton at C_3 which is trans to this same group. Similarly, in 1-methyl-2-phenylaziridine the proton at C_3 which is cis to the C_2 phenyl substituent is deshielded relative to the proton at C_3 which is trans to the same group.[12] The net result of the diamagnetic anisotropic effects of the aryl and carbonyl groups is that the ring protons of the cis isomers are shielded (or less strongly deshielded) relative to the corresponding trans isomers and are thus shifted to higher field. Similar chemical shift differences between protons α to the carbonyl groups of the cis and trans forms of 1-alkyl-2,3-diaroylaziridines[8] and 1,2-dibenzoylcyclopropanes[13] have been observed. The C_2 aryl substituent exerts a slight shielding effect on the methoxy carbonyl protons of the cis aziridine esters and also aids in assigning the proper stereochemical configuration in this series.

The multiplicities of the ring protons in the aziridine ketones are as anticipated for vicinal protons in which the chemical shift difference between the two nuclei is less than or equal to the coupling constant. Thus one observes either a single peak, a triplet, or a quartet. In contrast, the differences in chemical shift for C_2 H and C_3 H in the aziridine esters are sufficiently large (24–30 Hz) in comparison to J so that doublets are observed for each of these protons. Observed coupling constants of 7.0–7.5 and 2.5–3.0 Hz for the cis and trans aziridine esters, respectively, are of the same magnitude as reported for the analogous 1-alkyl-2-aryl-3-aroylaziridines.[7]

In contrast to the cis series, the ring proton spectra of the trans aziridines are greatly affected by the *N*-alkyl substituent and the effects, in turn, are solvent and temperature dependent. While the cis ring protons are sharp at 37° in chloroform solution, the trans isomers are broadened. Thus the half-widths of C_2 H are 1.0, 3.2, and 6.0 Hz for the trans aziridine ketones when the *N*-alkyl substituents are isopropyl (or cyclohexyl) ethyl (or benzyl) and methyl, respectively. At the same time the resonance signals from the methine, methylene, and methyl groups attached to the nitrogen atom are broadened to the extent that they appear as poorly resolved multiplets. In general, the C_2 H line width is greater than the line width of C_3H. This may be due to coupling of the C_2 H to the adjacent (ortho) protons of the C_2 aryl substituent. At 37° in carbon tetrachloride and benzene the line width of C_2 H in *trans*-1-ethyl-2(*p*-biphenyl)-3-benzoylaziridine (**9b**) is 1.4 and 1.6 Hz, respectively, while the line width in chloroform is 3.2 Hz. In addition, the methylene protons of the ethyl group appear as a slightly broadened quartet in carbon tetrachloride and benzene in contrast to the unresolved multiplet observed in chloroform solution. The appearance of the methylene resonance signals is not appreciably altered upon replacement of the proton at C_2 by deuterium.

The methylene protons of the *N*-benzyl group in *cis*- and *trans*-1-benzyl-2-phenyl-3-benzoylaziridine (**6a,b**) and methyl *cis*- and *trans*-1-benzyl-2-(*p*-biphenyl)-3-aziridine carboxylate (**12a,b**) are diastereotopic in all conformations and hence anisochronous.

The methylene protons in **6a** and **12a** appear as two distinct doublets (J = 14.0–15.0 Hz), whereas the methylene protons in **6b** and **12b** appear as broadened singlets.

The *N*-isopropyl methyl groups in *cis*- and *trans*-1-isopropyl-2-(*p*-biphenyl)-3-benzoylaziridine (**4a,b**) and *cis*- and *trans*-1-isopropyl-2-(*p*-biphenyl)-3-aziridinecarboxylate (**10a,b**) are also diastereotopic in all conformations. The methyl groups in **4a** and **10a**, however, appear as a doublet in deuteriochloroform, a broadened doublet in benzene, and two distinct doublets in carbon tetrachloride. In contrast, the methyl groups of the trans isomers **4b** and **10b** appear as two doublets in all of these solvents. The methine proton of the *N*-isopropyl group of **4a** and **10a** appears as a multiplet of at least nine lines in deuteriochloroform in comparison to the unresolved multiplet observed for this proton in **4b** and **10b**.

Variable-Temperature Proton Magnetic Resonance Spectra.—The partial pmr spectrum of *trans*-1-methyl-2-(*p*-biphenyl)-3-benzoylaziridine (**2b**) (Table I) appears in Figure 1. At 66°, the *N*-methyl protons appear as a singlet with a line width at half-height of 1.5 Hz. The ring protons at C_2 and C_3 exhibit a line width of

TABLE I

PMR SPECTRA OF *trans*-1-METHYL-2-(*p*-BIPHENYL)-3-BENZOYLAZIRIDINE[c]

Temp, °C	V_{H_2}[a] (width)[b]	V_{H_3}[a] (width)[b]	V_{CH_3}[a] (width)[b]	V'_{CH_3}[a,c]
66	215 (0.8)	206 (1.8)	159 (1.5)	
40	216 (1.0)	207 (3.5)	160 (3.6)	
37	215 (1.1)	206 (3.5)	160 (4.2)	
34	216 (1.5)	207	161 (4.6)	154
20	219 (1.8)	206 (2.2)	163 (1.8)	143
−6	220 (1.4)	207 (1.8)	163 (1.5)	140
−23	220 (1.2)	207 (1.8)	163 (1.5)	141

[a] Pmr spectra were determined on a Varian A-60D spectrometer with deuteriochloroform solutions. Chemical shifts are concentration independent and are reproducible within ±1 Hz. Tetramethylsilane (TMS) was the internal standard (0.0 Hz). All chemical shifts are given in hertz downfield relative to TMS. [b] Widths are line widths at half-heights and are expressed in hertz. [c] V' is the chemical shift in hertz of the methyl group of the minor invertomer.

(11) N. H. Cromwell, R. E. Bambury, and J. L. Adelfang, *J. Amer. Chem. Soc.*, **82**, 4241 (1960).

(12) S. J. Brois, *Tetrahedron*, **26**, 227 (1970).

(13) G. W. Griffin, E. J. O'Connell, and H. A. Hammond, *J. Amer. Chem. Soc.*, **85**, 1001 (1963).

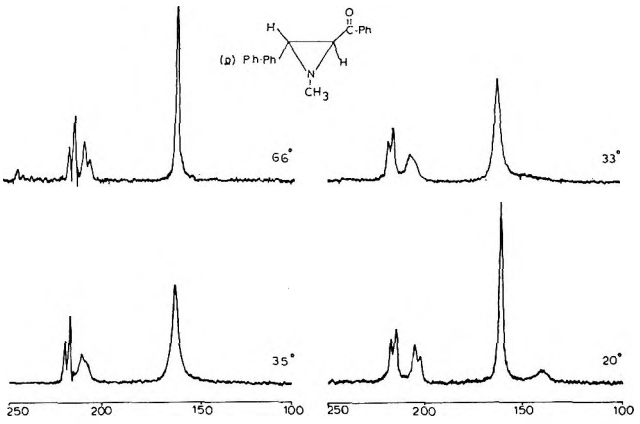


Figure 1.—Variable-temperature pmr spectra of *trans*-1-methyl-2-(*p*-biphenyl)-3-benzoylaziridine.

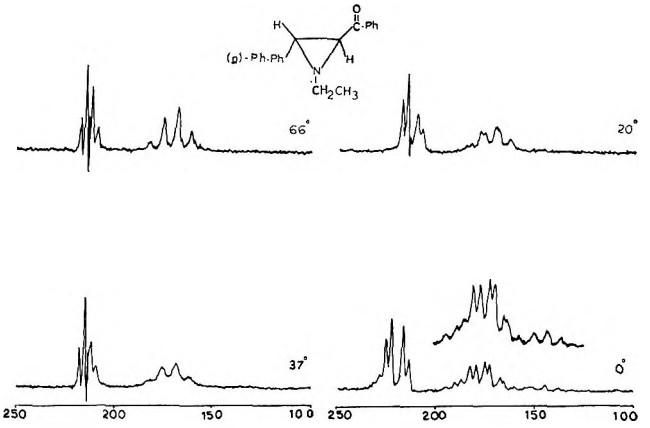


Figure 2.—Variable-temperature pmr spectra of *trans*-1-ethyl-2-(*p*-biphenyl)-3-benzoylaziridine.

1.8 and 0.8 Hz, respectively. Upon cooling to 37°, the line widths increase significantly to 4.2 Hz for the *N*-methyl resonance and 3.5 and 1.1 Hz for the ring protons at C_2 and C_3, respectively. When the temperature is lowered to 34°, the *N*-methyl signal is split into two separate broad peaks of unequal intensity. Further cooling results in a sharpening of these peaks and an increase in the chemical shift difference between them. The signals for the ring protons sharpen considerably. We feel that these observations can best be explained by the nitrogen inversion process. At 66° the rate of inversion is rapid and one observes an averaged signal for the two conformers (Scheme I). As the temperature is lowered the inversion rate is slowed. Hence at 37° the *N*-methyl signal has broadened by a factor of 2.8. Further cooling decreases the rate of inversion to the extent that the two separate *N*-methyl resonances appear, each resonance corresponding to one invertomer. Cooling to 20° and lower results in a further decrease in the inversion rate and hence a sharpening of the individual signals. At +2.0° the ratio of the two conformers is 83:17 by integration of the separate methyl resonances. Hence $\Delta F = -0.84$ kcal/mol (at 274°K). The ratio is constant, within experimental error, over the temperature range studied. As mentioned earlier, the ring protons in each conformer should appear as an AB or AX pattern. Unfortunately, the AB pattern corresponding to the ring protons in the minor invertomer are not resolved from the two doublets of the major conformer. There is a noticeable reproducible broadening downfield of the two sets of doublets of the major conformer which we believe is due to the ring protons of the minor conformer. Further support for this rationale was obtained by examination of the pmr spectrum of *trans*-1-ethyl-2-d_1-2-(*p*-biphenyl)-3-benzoylaziridine (**3'b**) at several temperatures. The proton at C_3 appeared as a singlet at 33° and higher temperature, but, when the spectrum was recorded at −31°, the signal was split into two peaks of unequal intensity. The smaller peak, which may be due to C_3 H of the minor conformer, appears downfield of the major resonance by approximately 2 Hz.

Figure 2 indicates that additional multiplicities are present, however. The methylene protons of the *N*-ethyl group are diastereotopic and hence will have different chemical shifts. This difference, however, may be small. The additional multiplicities observed may be due to slight changes in the relative chemical shifts of these protons with decreasing temperature.

Cooling may also slow the rate of rotation about the C–N bond resulting in nonequivalent methylene protons. An ABX_3 pattern would be observed for the ethyl group of each conformer in either case. We believe that the observed multiplicities of the methylene resonances and the spectra of **3'b** at lower temperatures are consistent with the presence of two detectable conformations (A and A') further complicated by nonequivalent methylene protons.

The pmr spectra of methyl *trans*-1-ethyl-2-(*p*-biphenyl)-3-aziridinecarboxylate (**9b**) over the temperature range studied resembles that of *N*-ethylaziridinyl ketone **4**. At 65° the methylene protons of the *N*-ethyl group appear as a sharp quartet. The ring protons appear as well-resolved doublets at 196 and 154 Hz for C_2 H and C_3 H, respectively. Cooling to 37° produces a broadening of both the ring protons and the methylene protons of the *N*-ethyl group. At 0° fine structure appears within the methylene protons resonance and additional multiplets appear 20 Hz upfield. Again we attribute the additional multiplicities to a decrease in the rate of inversion and to a nonequivalence of the methylene protons.

trans-1-Isopropyl-2-(*p*-biphenyl)-3-benzoylaziridine (**4b**) exhibits variable-temperature pmr spectra consistent with the other aziridinyl ketones and esters studied. At 66° the methine proton of the *N*-isopropyl group exhibits a sharp heptet. The ring protons appear as a sharp AB quartet. Cooling to 37° broadens the *N*-isopropyl methine resonance by a factor of 1.8. Further cooling to 0° produces a small broad resonance 47 Hz upfield from the methine resonance. While this broad resonance is reproducible at low temperatures (0 to −40°) and is not present at higher temperatures, it could not be resolved into individual lines. Nevertheless we believe that this upfield resonance is due to the methine proton of the *N*-isopropyl group of the minor conformer, while the heptet downfield which is sharp again at low temperatures is the analogous signal of the major conformer. The changes in ring proton spectra over the temperature range studied resemble the variations observed with the *trans*-*N*-methyl- and -*N*-ethylaziridinyl ketones.

The pmr spectrum of *trans*-1-benzyl-2-phenyl-3-benzoylaziridine (**6b**) at 70° yields a singlet at 244 Hz

for the benzyl protons. Upon cooling to 37° this sonance is considerably broadened. Further cooling to 20° produces a broad AB quartet (J_{AB} = 13.5 Hz). At 0° this quartet is considerably sharpened. The ring protons at 66° appear as an A_2 singlet at 217 Hz. Cooling, however, affects the chemical shift so that at 20° the ring protons appear as a AX pattern (two doublets). Examination of **6'b** (deuterium at C-2) results in a singlet for H-3 at 217 Hz. Upon cooling to 30° an additional singlet appears at 202 Hz which is of a minor intensity. Additionally a shoulder appears on the singlet at 217 Hz. The pmr spectrum of **6''b** (deuterium at C-2 and C-3) at 66° exhibits a singlet for the benzyl protons. Cooling to 20° results in an AB quartet for the benzyl protons and an additional singlet at 218 Hz which was masked by the ring protons in **6b** and **6'b**. We believe that the AB quartet for the benzyl protons is the result of magnetic nonequivalence resulting from restricted rotation about the *N*-benzyl C–N bond or slight changes in relative chemical shifts of the diastereotopic methylene protons with changing temperature. The singlet at 218 Hz in **6''b**, however, may be due to the benzylic protons of the minor conformer and results from a decrease in the rate of inversion. The singlet at 202 Hz in **6'b** is due to the proton at C_3 of the minor conformer.

The pmr spectrum of *cis*-1-benzyl-2-phenyl-3-benzoylaziridine (**6a**) gives an AB quartet (J = 13.8 Hz) for the benzylic protons at 66° and an AB triplet (J = 7.0 Hz) for the ring protons. Cooling to −20° changes the AB triplet of the ring protons to an AB quartet. We believe that this change is due only to a slight change in the relative chemical shifts of C_2 H and C_3 H and not to a slowed inversion process. Substitution of deuterium at C_2 resulted in a singlet for proton at C_3 at all temperatures.

Padwa[14] has reported the variable-temperature pmr spectra of *trans*-1-benzyl-2-phenyl-3-(*p*-tolyl)aziridine (**16b**). At high temperatures the ring protons appeared as an A_2 singlet. On cooling this singlet was split into two doublets of equal intensity. This spectral change was attributed to a slower rate of inversion at low temperature. The effects of temperature with regard to the *N*-benzyl group resonances were omitted. These results were compared with *trans*-1-benzyl-2,3-dibenzoylaziridine (**18b**). This may not be a valid comparison, however. The ring protons in **18b** are constitutionally equivalent if the inversion process is relatively fast. With a decrease in the rate of inversion, one would expect the ring protons to become nonequivalent, since one ring proton would be syn to the *N*-benzyl group and one anti. This would result in an AB quartet. The ring protons in **16b**, however, are constitutionally nonequivalent and it is simply fortuitous that they have the same chemical shift. It is not necessary that the relative chemical shifts of C_2 H and C_3 H remain constant with changing temperature (*e.g.*, see Table I). Hence the changes in the pmr spectra of **16b** with decreasing temperature may be due to small changes in the relative chemical shift of C_2 H and C_3 H and not to a decrease in the rate of nitrogen inversion. Our argument is strengthened since the pmr spectra of **6a** with decreasing temperature exhibits a similar spectral change, while the same compound with deuterium substituted at C_2 (**6'b**) showed no change with decreasing temperature. Additional peaks which are due to the nitrogen inversion process may be obscured and only be visible through deuterium labeling studies similar to those conducted for **6b**.

The pmr spectra of methyl *trans*-1-benzyl-2-(*p*-biphenyl)-3-aziridinecarboxylate (**12b**) is less complicated than the corresponding aziridinyl ketone, since the ring protons appear as an AX pattern (two doublets). The methylene protons of the *N*-benzyl group appear as a sharp singlet at 65°. Cooling to 37° produces a noticeable broadening of the methylene protons and broadening of the ring protons. The benzylic protons appear as an AB quartet (J = 12.5 Hz) at 10° while a singlet appears 20 Hz upfield. The AB quartet again is attributed to the diastereotopic methylene protons of the major conformer. The upfield singlet may be due to the diastereotopic methylene protons of the minor conformer.

Both methyl *trans*-1-*tert*-butyl-2-(*p*-biphenyl)-3-benzoylaziridinecarboxylate (**13b**) and *trans*-1-*tert*-butyl-2-phenyl-3-benzoylaziridine (**7b**) showed little change in their pmr spectra over the temperature range studied. This may be due to an inability to attain a sufficiently low temperature to slow the rate of inversion to the degree necessary for observation by pmr. This is not unexpected, since Roberts[3] has observed that the rate of inversion increased with the increase in the size of the *N*-alkyl group.

In general the pmr spectra of the *trans*-1-alkyl-2-aryl-3-benzoylaziridines and the methyl *trans*-1-alkyl-2-aroyl-3-aziridinecarboxylates at low temperatures exhibit a pattern consistent with the presence of two conformers. The protons of the *N*-alkyl group which are α to the nitrogen atom in the preferred conformation are 10–30 Hz downfield to the respective protons of the minor conformer. The carbonyl moiety, the C_2-aryl substituent, and the aziridine ring are all capable of exerting anisotropic effects on these protons. However, for either the carbonyl or the 2-aryl substituent to effectively shield these protons, the *N*-alkyl substituent must be syn to these groups. Replacement of the 2-phenyl substituent by methyl **15b** does not appreciably alter the magnitude of the shielding experienced by the cyclohexyl methine proton in *trans*-1-cyclohexyl-2-phenyl-3-benzoylaziridine (**5b**). However, reduction of this aziridine ketone to the corresponding aziridinecarbinol **20**[5] shifts the methine resonance upfield to an extent that it is now masked by the resonances of the other protons in the cyclohexane ring. The pmr spectra of *trans*-1-methyl-2,3-dibenzoylaziridine (**17b**) exhibits a resonance at 157 Hz which is attributed to the *N*-methyl resonance. One will note that the *N*-methyl group must be syn to a benzoyl group and hence will be influenced by the carbonyl moiety. The major conformer of *trans*-1-methyl-2-(*p*-biphenyl)-3-benzoylaziridine (**2b**) exhibits a resonance at 162 Hz which is attributed to the *N*-methyl group. Reduction of the above *N*-methylaziridine **2b** with lithium aluminum hydride produced a single aziridinecarbinol **19**. The pmr spectrum of this carbinol exhibited an *N*-methyl resonance at 128 Hz which was 34 Hz upfield from the *N*-methyl resonance of the corresponding aziridine ketone. These results seem to indicate that the preferred conformation of **2b** is the conformer with the

(14) A. Padwa and L. Hamilton, *J. Amer. Chem. Soc.*, **89**, 105 (1967).

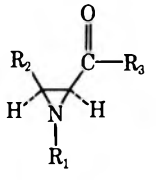
N-alkyl group and the benzoyl occupying a syn relationship (structure A, Scheme I). Further, the fact that in the other trans aziridine ketones and aziridine esters whose pmr spectra were temperature dependent, the protons α to the nitrogen of the *N*-alkyl substituent were at lower field in the major conformer. This seems to indicate that the preferred conformation may be that in which the *N*-alkyl substituent is syn to the carbonyl moiety. Sterically there appears to be little difference between the two conformers (A and A′). In conformer A′, however, the nitrogen lone pair is in close proximity to the nonbonded electrons of the carbonyl group. Such an electronic interaction may be sufficient to destabilize A′. In conformer A, on the other hand, the nitrogen lone pair and the nonbonded electrons of the carbonyl group are situated in a manner as to minimize these interactions.

The pmr spectra of the analogous *cis*-aziridinyl ketones and methyl *cis*-aziridinecarboxylates studied, however, exhibited only slight changes with decreasing temperature. This may be due to failure to lower the temperature sufficiently to slow the rate of inversion. A second explanation, however, seems more reasonable. Conformer B (see Scheme II) would be expected to be greatly favored over conformer B′ from steric considerations. If the equilibrium concentration of B′ is very low relative to B, conformer B′ would not be observed by pmr even if the temperature was lowered to sufficiently slow the rate of inversion.

Inspection of the chemical shifts of the ring protons of the *cis*-aziridinyl ketones and methyl *cis*-aziridinecarboxylates (Table II) indicates a downfield shift in

TABLE II

CHEMICAL SHIFTS OF RING PROTONS AND PROTONS α TO THE NITROGEN OF THE *N*-ALKYL GROUP IN THE CIS AZIRIDINES[a]



Compd	R_1	R_2	R_3	—Chemical shift, Hz— H_α	H_2	H_3
2a	CH_3	Ar[b]	Ph[b]	152	183	193
3a	C_2H_5	Ar	Ph	156[d]	184	194[c]
4a	*i*-C_3H_7	Ar	Ph	111	188	197
5a	C_6H_{11}	Ph	Ph	60–120[e]	187	197[c]
6a	CH_2Ph	Ph	Ph	220, 235[d]	192	199
7a	*tert*-C_4H_9	Ph	Ph		205	205
9a	C_2H_5	Ar	OCH_3	150[d]	174	150[c]
10a	*i*-C_3H_7	Ar	OCH_3	100	174	154
11a	C_6H_{11}	Ar	OCH_3	60–120[f]	175	155[c]
12a	CH_2Ph	Ar	OCH_3	215, 236[d]	182	159
13a	*tert*-C_4H_9	Ar	OCH_3		190	162[c]

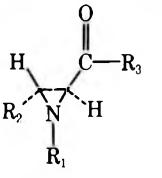
[a] Pmr spectra were determined on a Varian Associates Model A-60 or A-60D spectrometer at 37° in deuteriochloroform. Chemical shifts are given in hertz downfield from tetramethylsilane, an internal standard. For compound preparation, see for **2a**, **5a**, and **6a**, ref 9; **7a**, ref 20; **10a** and **11a**, ref 6a; other aziridines, this paper. [b] Ar = *p*-biphenyl; Ph = phenyl. [c] The assignment of the ring protons was established by preparation of these compounds with deuterium at C_2. [d] Nonequivalent methylene protons. [e] Methine proton masked by cyclohexyl methylene envelope. [f] See ref 3.

both C_2 H and C_3 H as the size of the *N*-alkyl group is varied (*i.e.*, Me < Et < *i*-Pr ~ C_6H_{11} ≪ *tert*-Bu). This downfield shift seems to be a function of steric crowding on the α carbon of the *N*-alkyl group. Hence the sterically bulky *tert*-butyl group is responsible for the largest downfield shift. This shift may be due to intramolecular van der Waals dispersion effects.[15] Such effects have also been noted recently by Brois[12] in *N*-alkylaziridines and *N*-alkylstyrenimines.

Careful examination of the chemical shifts of the trans isomers (Table III) indicates that the C_2 H is

TABLE III

CHEMICAL SHIFTS OF RING PROTONS AND PROTONS TO THE NITROGEN OF THE *N*-ALKYL GROUP IN THE TRANS AZIRIDINES[a]



Compd	R_1	R_2	R_3	—Chemical shift, Hz— H	H_2	H_3
1b	H	Ar[b]	Ph[b]	163	191	213[c]
2b	CH_3	Ar	Ph	160	202	213
17b	CH_3	PhCO	Ph	157	238	238
3b	C_2H_5	Ar	Ph	173	211	217[c]
4b	*i*-C_3H_7	Ar	Ph	181	215	220
15b	C_6H_{11}	CH_3	Ar	127	161	199
5b	C_6H_{11}	Ph	Ph	127	214	218[c]
6b	CH_2Ph	Ph	Ph	242	217	217[c]
7b	*tert*-C_4H_9	Ph	Ph		231	204[c]
9b	C_2H_5	Ar	OCH_3	186	195	165[c]
10b	*i*-C_3H_7	Ar	OCH_3	181	195	164
11b	C_6H_{11}	Ar	OCH_3	128	196	164
12b	CH_2Ph	Ar	OCH_3	240	198	163
13b	*tert*-C_4H_9	Ar	OCH_3		218	165

[a] Pmr spectra were determined on a Varian Associates Model A-60 or A-60D spectrometer in deuteriochloroform at 37°. Chemical shifts are given in hertz downfield from tetramethylsilane (TMS). Chemical shifts are reproducible to ±1 Hz. For compound preparation, see for **5b** and **6b**, ref 9; **7b**, A. Padwa and W. Eisenhardt, *J. Amer. Chem. Soc.*, **90**, 2442 (1968); **15b**, N. H. Cromwell and R. J. Mohrbacher, *ibid.*, **75**, 6252 (1953); **17b**, ref 8; **10b** and **11b**, ref 6a; other aziridines, this paper. [b] Ar = *p*-biphenyl, Ph = phenyl. [c] The assignment of the ring protons was established by preparation of these compounds with deuterium at C_2.

shifted downfield as the size of the nitrogen substituent is increased from methyl to *tert*-butyl. This downfield shift again can be attributed to an intramolecular van der Waals dispersion effect[14] if one assumes that the trans isomers exist in a preferred conformation in which the substituent on nitrogen is syn to the carbonyl group and C_2 H. This is in agreement with the low-temperature pmr studies discussed earlier. Concomitant with the large deshielding effect of the bulky *tert*-butyl group is an apparent shielding effect on C_3 H which is anti to the *tert*-butyl group. This effect is much larger in the aziridinyl ketones than in the methylaziridinyl esters. A similar effect was noted by Brois[15] and was attributed to a distortion of the electron cloud away from the substituents syn to the *tert*-butyl group and toward the substituents on the opposite side of the ring. In contrast to the observations of Brois,[15] however, is the downfield shift of the ring protons when the substituent on the

(15) For a discussion of these effects see L. M. Jackman and S. Sternhell, "Application of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed, Pergamon Press, New York, N. Y., 1969, p 71.

nitrogen is changed from hydrogen to methyl. Brois observed an opposite effect and attributed it to the anisotropy of the C–N bond of the alkyl group. Our systems seem to indicate a deshielding effect similar to a dispersion effect in going from hydrogen to methyl, although the magnitude of this effect is much larger than would be expected.

Experimental Section

Melting points were determined by the capillary method and are uncorrected. Elemental analyses were performed by Micro-Tech Laboratories, Skokie, Ill. The infrared spectra were determined on Perkin-Elmer Model 237 or 621 instruments. The 60-MHz nmr spectra were determined on Varian A-60 or A-60D spectrometers and the chemical shifts are reported in parts per million (δ) relative to internal tetramethylsilane (δ 0.0).

A. Synthesis of Aziridine Ketones. Preparation of β-(p-Biphenyl)-β-methoxyaminopropiophenone (21).—By a modification of a previously published procedure,[16] 0.47 g (10 mmol) of methoxyamine[17] was added to a suspension of 2.50 g (8.7 mmol) of *trans*-4-phenylchalcone[18] in 20 ml of methanol. The suspension was warmed slightly below reflux for 5.5 hr. The reaction mixture was cooled and 2.56 g (88%) of **21** was collected. Recrystallization from ethanol gave white plates: mp 81–82°; ir (KBr) $\nu_{C=O}$ 1675 cm^{-1}; pmr ($CDCl_3$) δ 3.36 (d, J = 5.5 Hz, 2 H, C_α H), 3.45 (s, 3 H, $-OCH_3$), 4.72 (t, J = 5.5 Hz, 1 H, C_β H), 6.02 (br s, 1 H, NH), and 7.18–8.19 (m, 14 H, aromatic).

Anal. Calcd for $C_{22}H_{21}O_2N$: C, 79.73; H, 6.29; N, 4.23. Found: C, 79.64; H, 6.32; N, 4.34.

***trans*-2-(p-Biphenyl)-3-benzoylaziridine (1b).**—By a modification of a previously published procedure,[16] 0.36 g (6.67 mmol) of sodium methoxide in methanol was added dropwise to a warm solution of 1.12 g (3.38 mmol) of **21** in 70 ml of methanol. After stirring for 2 hr, the resultant red solution was cooled, yielding 0.92 g (90.7%) of an orange solid. The solid was dissolved in ether and washed free of base. The ether solution was dried ($MgSO_4$) and concentrated, and the residue recrystallized from ethanol giving **1b** as white needles: mp 117–118°; ir (KBr) $\nu_{C=O}$ 1662 cm^{-1}; pmr ($CDCl_3$) δ 2.72 (br s, 1 H, NH), 3.19 (br d, J = 2.3 Hz, 1 H, C_2 H), 3.55 (d, J = 2.3 Hz, 1 H, C_3 H), and 7.23–8.14 (m, 14 H, aromatic).

Anal. Calcd for $C_{21}H_{17}NO$: C, 84.25; H, 5.73; N, 4.68. Found: C, 84.05; H, 5.70; N, 4.78.

***trans*-1-Methyl-2-(p-biphenyl)-3-benzoylaziridine (2b).**—Methylamine (0.76 g, 25 mmol) was dissolved in 50 ml of ether cooled to 0°. To this solution were added 1.27 g (5.0 mmol) of iodine and 1.44 g (5.0 mmol) of *trans*-4-phenylchalcone.[18] After stirring for 6 hr at room temperature, the reaction mixture was diluted with benzene. The precipitated amine salt was removed by filtration and the filtrate was washed with water. The dried ($MgSO_4$) filtrate was concentrated and the pale yellow residue was recrystallized from ether to afford 1.25 g (80%) of *trans*-1-methyl-2-(*p*-biphenyl)-3-benzoylaziridine (**2b**): mp 100–101°; pmr ($CDCl_3$) δ 2.66 (br s, 3 H, methyl), 3.36 (br, s, 1 H, C_2 H), 3.55 (d, J = 2.6 Hz, 1 H, C_3 H), 7.2–7.7 and 7.9–8.1 (two m, 14 H, aromatic); ir (CCl_4) $\nu_{C=O}$ 1675 cm^{-1}.

Anal. Calcd for $C_{22}H_{19}NO$: C, 84.31; H, 6.11; N, 4.47. Found: C, 84.39; H, 6.29; N, 4.44.

1-Ethyl-2-(p-biphenyl)-3-benzoylaziridine, *cis* and *trans* (3a,b).—A solution of 1.27 g (5.0 mmol) of iodine and 1.2 g (25.0 mmol) of ethylamine in 25 ml of benzene was stirred at 10° while 1.42 g (5.0 mmol) of 4-phenylchalcone[18] was added. Stirring was continued until the initial yellow-red color was discharged (2–4 hr). Work-up according to the procedure described above gave a pale yellow solid which was recrystallized from methanol. *trans*-1-Ethyl-2-(*p*-biphenyl)-3-benzoylaziridine (**3b**), mp 96–97°, was obtained in 60% yield: pmr ($CDCl_3$) δ 1.10 (t, J = 7.0 Hz, 3 H, methyl), 2.86 (br q, J = 7 Hz, 2 H, methylene), 3.51 (br d, J = 2.7 Hz, 1 H, C_2 H), 3.61 (d, J = 2.7 Hz, 1 H, C_3 H), 7.1–7.6 and 7.8–8.0 (two m, 14 H, aromatic); ir (CCl_4) $\nu_{C=O}$ 1673 cm^{-1}.

Anal. Calcd for $C_{23}H_{21}NO$: C, 84.37; H, 6.47; N, 4.28; mol wt, 327.41. Found: C, 84.12; H, 6.49; N, 4.20; mol wt, 327 (mass spectrum).

The residue remaining after evaporation of the methanol filtrate was extracted several times with hot petroleum ether (bp 30–60°) and the insoluble material was recrystallized from ether–petroleum ether (1:1, v/v) to afford a pure sample of the corresponding cis aziridine: mp 109–111°; pmr ($CDCl_3$) δ 1.27 (t, J = 7.4 Hz, 3 H, methyl), 2.13–2.96 (m, 2 H, methylene), 3.06 (d, J = 7.3 Hz, 1 H, C_2H), 3.23 (d, J = 7.4 Hz, 1 H, C_3 H), 7.0–7.5 and 7.8–8.0 (two m, 14 H, aromatic); ir (CCl_4) $\nu_{C=O}$ 1670 and 1691 cm^{-1}.

Anal. Found: C, 84.32; H, 6.59; N, 4.31; mol wt, 327 (mass spectrum).

The cis/trans ratio was *ca.* 1:4 as determined from the pmr spectrum of the crude material.

1-Isopropyl-2-(p-biphenyl)-3-benzoylaziridine, *cis* and *trans* (4a,b) were produced by reaction of 4-phenylchalcone[18] (1.42 g, 5.0 mmol) with a mixture of 1.27 g (5.0 mmol) of iodine and isopropylamine (1.37 g, 25.0 mmol) in 25 ml of benzene. After work-up of the reaction mixture according to the above procedure, the crude material was extracted twice with hot petroleum ether. The residue was recrystallized from the same solvent to afford 0.35 g (26%) of pure *cis*-1-isopropyl-2-(*p*-biphenyl)-3-benzoylaziridine (**4a**): mp 108–110°; pmr ($CDCl_3$) δ 1.26 (d, J = 6.1 Hz, 6 H, isopropyl methyls), 1.85 (m, 1 H, isopropyl methine), 3.13 (d, J = 7.4 Hz, 1 H, C_2 H), 3.28 (d, J = 7.3 Hz, 1 H, C_3 H), 7.0–7.5 and 7.8–8.0 (two m, 14 H, aromatic); ir (CCl_4) $\nu_{C=O}$ 1670 and 1695 cm^{-1}.

Anal. Calcd for $C_{24}H_{23}NO$: C, 84.42; H, 6.79; N, 4.10; mol wt, 341.43. Found: C, 84.14; H, 6.87; N, 3.90; mol wt, 341 (mass spectrum).

The combined petroleum ether extracts were evaporated. The residue was diluted with pentane and cooled to produce a pale yellow solid. Recrystallization of this material from a minimal amount of methanol afforded 1.0 g (74%) of the corresponding trans aziridine (**4b**): mp 83–85°; pmr ($CDCl_3$) δ 0.94 and 1.21 (two d, J = 6.3 Hz, 3 H, each, isopropyl methyls), 3.59 (br d, J = 2.8 Hz, 1 H, C_2 H), 3.66 (d, J = 2.8 Hz, 1 H, C_3 H), 7.2–7.7 and 8.0–8.2 (two m, 14 H, aromatic); ir (CCl_4) $\nu_{C=O}$ 1673 cm^{-1}.

Anal. Found: C, 84.28; H, 6.78; N, 4.12; mol wt, 341 (mass spectrum).

The two aziridines were obtained in an overall yield of 80%.

B. Synthesis of Deuterium Labeled 1-H and 1-Alkyl-2-aryl-3-aroylaziridines. ***trans*-2-d_1-2-(p-Biphenyl)-3-benzoylaziridine (1′b).**—Base-catalyzed condensation of *p*-phenylbenzaldehyde-d_1 with acetophenone afforded 1-(*p*-biphenyl)-3-d_1-3-phenyl-2-propen-1-one (β-d_1-4-phenylchalcone), mp 109–110° (lit.[18] 110°). Reaction of labeled 4-phenylchalcone with methoxyamine followed by ring closure with sodium methoxide as described for **1b** gave **1′b**. Mixture melting point determination with **1b** showed no depression. The ring proton spectra consisted of a singlet at δ 3.55.

1-Ethyl-2-d_1-2-(p-biphenyl)-3-benzoylaziridine, *cis* and *trans* (3′a,b).—Bromination and subsequent dehydrohalogenation of β-d_1-4-phenylchalcone with *N*-methylpiperidine afforded 1-phenyl-2-bromo-3-d_1-3-(*p*-biphenyl)-2-propen-1-one (α-bromo-β-d_1-4-phenylchalcone), mp 29–31° (lit.[18] 30–31°). Reaction of the labeled α-bromo-4-phenylchalcone with ethylamine as previously described produced **3′a** and **3′b**. The ring proton spectra of **3′a** and **3′b** consisted of singlets at δ 3.23 and 3.61, respectively.

1-Cyclohexyl-2-d_1-2-phenyl-3-benzoylaziridine was produced as a mixture of the cis and trans (**5′a,b**) forms by treatment of the deuterium labeled α-bromochalcone with 2 equiv of cyclohexylamine in benzene. The isomeric aziridines were separated by fractional crystallization. Mixture melting point experiments with unlabeled samples showed no depression. The pmr spectrum ($CDCl_3$) confirmed the introduction of deuterium at C_2. Thus singlets were observed at δ 3.28 and 3.63 for the cis and trans forms, respectively.

1-*tert*-Butyl-2-d_1-2-phenyl-3-benzoylaziridine, *cis* and *trans* (7′a,b).—Base-catalyzed condensation of benzaldehyde-d_1 with acetophenone afforded 1,3-diphenyl-3-d_1-2-propen-1-one (β-d_1-chalcone), mp 56–57° (lit.[19] 58°). Reaction of β-d_1-chalcone with 1 equiv of iodine and 5 equiv of *tert*-butylamine in methanol for

(16) The procedure was developed by A. H. Blatt, *J. Amer. Chem. Soc.*, **61**, 3494 (1939); however, the structure of the product was incorrectly assigned as an α-amino-α,β-unsaturated ketone. Later N. H. Cromwell, *et al.*, *ibid.*, **73**, 1044 (1951), correctly assigned the structure as the isomeric aziridine.

(17) M. Davies and N. A. Spears, *J. Chem. Soc.*, 3987 (1959).

(18) N. H. Cromwell, *et al.*, *J. Amer. Chem. Soc.*, **65**, 301 (1943).

(19) E. P. Kohler and H. M. Chadwell in "Organic Syntheses," Collect. Vol. IV, 2nd ed, A. H. Blatt, Ed., Wiley, New York, N. Y., 1941, p 78.

24 hr at room temperature with work-up in the usual manner produced a pale yellow oil. Column chromatography on silica gel and elution with 5% ether–petroleum ether produced the labeled trans isomer **7'b**. The ring proton spectra consisted of a singlet at δ 3.40. A mixture melting point with unlabeled compound showed no depression.

Elution with 15% ether–petroleum ether produced the cis isomer **7'a**. The ring proton spectra consisted of a singlet at δ 3.41. Mixture melting point with unlabeled compound showed no depression.

1-Benzyl-2-d_1-2-phenyl-3-benzoylaziridine, *cis* and *trans* (6'a,b).—Treatment of α-bromo-β-d_1-chalcone with 2 equiv of benzylamine in methanol yielded the isomeric aziridines. Column chromatography on silica gel eluting with 5% ether–petroleum ether produced **6'b**. Continued elution with 15% ether–petroleum ether produced **6'a**. Mixture melting points with unlabeled compounds showed no depressions. Pmr ring proton spectra of **6'a** and **6'b** showed singlets at δ 3.32 and 3.62, respectively.

1-Benzyl-2,3-d_2-2-phenyl-3-benzoylaziridine, *cis* and *trans* (6''a,b).—Treatment of α-bromo-β-d_1-chalcone with 3 equiv of benzylamine-d_2 in benzene with work-up and separation as above produced **6''a** and **6''b**.

C. Synthesis of Methyl *cis*- and *trans*-1-Alkyl-2-(*p*-biphenyl)-3-aziridinecarboxylates. Methyl 1-Ethyl 2-(*p*-biphenyl)-3-aziridinecarboxylate, *cis* and *trans* (9a,b).—A stirred suspension of 2.0 g (5.0 mmol) of methyl *trans*-α-bromo-*p*-phenylcinnamate[6b] (**22**) in 50 ml of methanol was cooled to 0° and treated with 3.4 g (75.0 mmol) of ethylamine. The reaction mixture was allowed to warm to room temperature. After stirring for 24 hr all solids had dissolved. The solvent and excess amine were removed under reduced pressure without heating. The residue was diluted with ether and the precipitated amine salt was collected. The filtrate was washed with water and dried (anhydrous $MgSO_4$), and the solvent was removed under reduced pressure. The residual oil was chromatographed on silica gel (80 g) and eluted successively with petroleum ether (500 ml) and ether–petroleum ether mixtures (1:49, 500 ml; 1:9, 500 ml; 15:85, 1 l.). The latter fractions afforded 0.15 g (16%) of methyl *trans*-1-ethyl-2-(*p*-biphenyl)-3-aziridinecarboxylate (**9b**): mp 89–91°; pmr ($CDCl_3$) δ 1.13 (t, J = 7.3 Hz, 3 H, methyl), 2.75 (d, J = 2.4 Hz, 1 H, C_3 H), 3.25 (br s) and 3.4–2.8 (m, 3 H, C_2 H and methylene, respectively), 3.80 (s, 3 H, methoxy), and 7.3–7.7 (m, 9 H, aromatic); ir (CCl_4) $\nu_{C=O}$ 1733 cm^{-1}.

Anal. Calcd for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98. Found: C, 76.79; H, 6.88; N, 4.90.

Further elution with 20% ether–petroleum ether gave 0.80 g (84%) of a colorless oil which eventually crystallized upon standing in the freezer, mp <5°. This material was assigned the structure methyl *cis*-1-ethyl-2-(*p*-biphenyl)-3-aziridinecarboxylate (**9a**) on the following data: pmr ($CDCl_3$) δ 1.24 (t, J = 7.0 Hz, 3 H, methyl), 2.50 and-2.90 [two d, superimposed on a multiplet of 12 lines, 2.1–2.9 (4 H, C_3 H, C_2 H, and methylene, respectively)], 3.48 (s, 3 H, methoxy), and 7.3–7.8 (m, 9 H, aromatic); ir (neat) $\nu_{C=O}$ 1725 and 1750 cm^{-1}.

Anal. Found: C, 76.96; H, 6.59; N, 5.02.

Methyl 1-Benzyl-2-(*p*-biphenyl)-3-aziridinecarboxylate, *cis* and *trans* (12a,b).—A solution of 0.48 g (0.15 mmol) of **22**, 2.40 g (2.25 mmol) of benzylamine, and 12 ml of methanol was stirred at room temperature for 48 hr. The pale yellow oil obtained after work-up as in **9a,b** was chromatographed on silica gel. Elution with 2% ether–petroleum ether yielded 121 mg (23%) of **12b** as a colorless oil which was crystallized from petroleum ether (bp 60–70°): mp 64–65°; pmr ($CDCl_3$) δ 2.72 (d, J = 2.5 Hz, 1 H, C_3 H), 3.31 (br s, 1 H, C_2 H), 3.57 (s, 3 H, methoxy), 4.00 (br s, 2 H, benzylic), and 6.95–7.45 (m, 9 H, aromatic); ir (KBr) $\nu_{C=O}$ 1724 cm^{-1}.

Anal. Calcd for $C_{23}H_{21}NO_2$: C, 81.69; H, 5.74; N, 3.82. Found: C, 81.80; H, 5.69; N, 3.92.

Continued elution with 20% ether–petroleum ether yielded 371 mg (72%) of **12a**: mp 149–150°; pmr ($CDCl_3$) δ 2.65 (d, J = 6.5 Hz, 1 H, C_3 H), 3.03 (d, J = 6.5 Hz, 1 H, C_2 H), 3.49 (s, 3 H, methoxy), 3.80 (d of d, J = 14.0 Hz, 2 H, benzylic), and 7.15–7.75 (m, 9 H, aromatic); ir (KBr) $\nu_{C=O}$ 1741 cm^{-1}.

Anal. Found: C, 81.92; H, 5.72; N, 3.86.

Methyl 1-*tert*-Butyl-2-(*p*-biphenyl)-3-aziridinecarboxylate, *cis* and *trans* (13a,b).—A solution of **22** (1.59 g, 5.0 mmol) was dissolved in 7.3 g (0.10 mol) of *tert*-butylamine and 25 ml of acetonitrile and stirred for 5 days. A pale oil obtained after work-up as in **9a,b** was dissolved in methanol and 0.70 g (44%) of **22** was filtered off. After removal of the methanol from the filtrate, the resultant oil was chromatographed on silica gel. Elution with petroleum ether (bp 60–70°) followed by elution with 2% ether–petroleum ether afforded 150 mg (10%) of **13b** as a colorless oil which was crystallized from *n*-pentane: mp 79–81°; pmr ($CDCl_3$) δ 1.15 (s, 9 H, three methyls), 2.75 and 3.63 (two d, J = 2.5 Hz, 1 H each, C_3 H and C_2 H, respectively), 3.83 (s, 3 H, methoxy), and 7.1–7.6 (m, 9 H, aromatic); ir (KBr) $\nu_{C=O}$ 1727 cm^{-1}.

Anal. Calcd for $C_{20}H_{23}NO_2$: C, 77.64; H, 7.49; N, 4.53. Found: C, 77.82; H, 7.47; N, 4.54.

Continued elution with 2% ether–petroleum ether afforded 325 mg (21%) of **13a** as a colorless oil which was crystallized from pentane: mp 88–90°; pmr ($CDCl_3$) δ 1.10 (s, 9 H, three methyls), 2.70 and 3.17 (two d, J = 6.5 Hz, 1 H each, C_3 H and C_2 H, respectively), 3.45 (s, 3 H, methoxy), and 7.2–7.7 (m, 9 H, aromatic); ir (CCl_4) $\nu_{C=O}$ 1755 and 1725 cm^{-1}.

Anal. Found: C, 77.62; H, 7.55; N, 4.57.

D. Synthesis of Deuterium Labeled Methyl 1-Alkyl-2-(*p*-biphenyl)-3-aziridinecarboxylates. Methyl 1-Ethyl-2-d_1-2-(*p*-biphenyl)-3-aziridinecarboxylate, *cis* and *trans* (9'a,b).—These compounds were prepared by the reaction of methyl *trans*-α-bromo-β-d_1-*p*-phenylcinnamate[6b] and a 15-fold excess of ethylamine in methanol. The products were isolated as described for **9a,b**. The ring proton spectra of these deuterium labeled aziridines appeared as singlets at 150 and 165 Hz for **9'a** and **9'b**, respectively, and confirmed the ring proton assignments.

Methyl 1-*tert*-Butyl-2-d_1-2-(*p*-biphenyl)-3-aziridinecarboxylate, *cis* and *trans* (13'a,b).—These products were prepared by the reaction of methyl *trans*-α-bromo-β-d_1-*p*-phenylcinnamate with a 15-fold excess of *tert*-butylamine. Products were isolated as in **13a** and **13b**. The ring proton spectra of **13'a** and **13'b** consisted of singlets at 162 and 165 Hz, respectively, and confirmed the ring proton assignments.

Reduction of 1b with Lithium Aluminum Hydride.—A solution of 376 mg (1.16 mmol) of the *N*-methylaziridine **1b** in 5 ml of dry benzene was added dropwise to a stirred suspension of 100 mg (2.63 mmol) of $LiAlH_4$ in 20 ml of dry ether. After the addition, the solution was refluxed for 4 hr. The excess $LiAlH_4$ was neutralized with water and 15% sodium hydroxide solution. The resultant precipitate was filtered and the filtrate was concentrated. Recrystallization of the resultant pale yellow crystals from petroleum ether afforded 45% of *trans*-1-methyl-2-(*p*-biphenyl)-3-(α-hydroxybenzyl)aziridine: mp 142–143°; pmr ($CDCl_3$) δ 2.18 (br s, 3 H, NCH_3), 2.35 (m, 1 H, C_3 H), 3.40 (br s, 2 H, C_2 H and OH), 4.93 (d, J = 4.0 Hz, 1 H, –CHOHPh), and 7.1–7.6 (m, 14 H, aromatic).

Anal. Calcd for $C_{22}H_{21}NO$: C, 83.80; H, 6.67; N, 4.44. Found: C, 83.98; H, 6.64; N, 4.50.

Registry No.—**1b**, 32044-30-7; **2a**, 32044-31-8; **2b**, 32044-32-9; **3a**, 32044-33-0; **3b**, 32044-34-1; **4a**, 32044-35-2; **4b**, 32044-36-3; **5a**, 2211-65-6; **5b**, 2211-61-2; **6a**, 6372-57-2; **6b**, 6476-12-6; **7a**, 20847-26-1; **7b**, 20847-27-2; **9a**, 32044-41-0; **9b**, 32044-42-1; **10a**, 23214-21-3; **10b**, 23214-22-4; **11a**, 32044-45-4; **11b**, 23214-20-2; **12a**, 32044-47-6; **12b**, 32044-48-7; **13a**, 32087-72-2; **13b**, 32044-49-8; **15b**, 32044-50-1; **17b**, 793-02-2; **21**, 32044-52-3; *trans*-1-methyl-2-(*p*-biphenyl)-3-(α-hydroxybenzyl)aziridine, 32044-53-4.

Acknowledgment.—This work was supported in part by the National Cancer Institute, USPH Grant No. CA-02931, and the Petroleum Research Foundation.

Mobile Keto Allyl Systems. XI.[1] Kinetic Studies of the Rearrangement–Substitution Reactions of *trans*-β-Benzoyl-γ-phenylallyl Halides

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Received May 11, 1971

The kinetics of the reactions of *trans*-β-benzoyl-γ-phenylallyl bromide (1a) and the corresponding chloride (1b) with six primary and secondary amines in *n*-hexane solution are reported. The rate data and product studies indicate that the reactions are bimolecular rearrangement–substitutions. A retardation in the reaction rate with 1a is observed with increasing bulk at the α-carbon atom of the amine. The leaving group effect suggests a rate-limiting transition state in which there is only a small extension of the carbon–halogen bond.

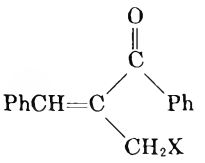
Primary allyl halides have been observed to react with amines to give mainly the normal substitution products.[3] However, it was reported recently that compounds **1a** and **1b** with primary and secondary amines gave exclusively the rearranged substitution products under suitable conditions.[4] Previous work from this laboratory has shown that a secondary halide, 3-bromo-2-benzal-1-indanone, also reacts with primary and secondary amines to give the abnormal substitution products.[5]

It was suggested, as a result of kinetic studies, that, in these reactions of the secondary halide, bond development and bond cleavage were virtually concerted, with some charge localization at the carbonyl group in the transition state.[6] A dipolar transition state structure was also proposed for the reactions of 2-[(α-substituted amino)benzyl]acrylophenones with amines.[7]

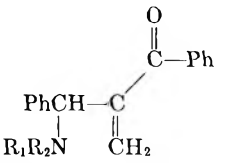
The mechanisms of the abnormal nucleophilic substitution reactions of β-benzoyl-γ-phenylallyl halides were of interest to us, and in these initial studies we have investigated the reactions of the bromide **1a** and of the chloride **1b** with primary and secondary amines in order to measure their sensitivity to changes in the size and nucleophilicity of the amine and in the nature of the leaving group.

Results

trans-β-Benzoyl-γ-phenylallyl bromide and chloride react with primary and secondary amines in nonpolar solvents to give the corresponding 2-[α-(substituted amino)benzyl]acrylophenones.[4] Product and kinetic studies were made in *n*-hexane solution of the reactions of **1a** with *N*-methylcyclohexylamine, cyclohexylamine, piperidine, morpholine, *tert*-butylamine, and triethylcarbinylamine and of **1b** with cyclohexylamine and triethylcarbinylamine. It was established within experimental error that the amount of halide ion produced was equivalent to the yield of abnormal substitution product (**2a–f**).



1a, X = Br
b, X = Cl
c, X = *N*-methylcyclohexylamino



2a, R_1R_2N = *N*-methylcyclohexylamino
b, R_1R_2N = cyclohexylamino
c, R_1R_2N = piperidino
d, R_1R_2N = morpholino
e, R_1R_2N = *tert*-BuNH–
f, R_1R_2N = Et_3CNH–

When stoichiometric quantities of **1a** and *N*-methylcyclohexylamine were allowed to react for 66 hr at room temperature, a pmr spectrum of the crude product indicated the presence of a 1:1 mixture of **2a** and **1c**. Dropwise addition of the amine to **1a** over 24 hr resulted in a 91% yield of **2a**, indicating that **1c** resulted from the further reaction of **2a** with amine.[7]

The rates of reaction of **1a** with the six amines over a range of concentrations of nucleophile and of **1a** were estimated by analysis for bromide ion. The results are given in Table I. Each of the reactions exhibited

TABLE I

VALUES OF THE SECOND-ORDER RATE COEFFICIENTS k_2 FOR THE REACTIONS OF β-BENZOYL-γ-PHENYLALLYL BROMIDE WITH AMINES IN HEXANE AT 25°

Amine	10^3[amine]	10^3[allyl bromide]	10^2k_2, l. mol^{-1} sec^{-1}
Cyclohexylamine	19.02	5.330	1.32 ± 0.08[a]
	19.02	6.240	1.31 ± 0.08
	14.45	5.330	1.21 ± 0.09
	14.23	5.328	1.29 ± 0.01
	27.50	5.328	1.27 ± 0.06
	27.50	6.076	1.30 ± 0.05
Morpholine	15.54	6.072	6.38 ± 0.04
	15.54	6.368	7.05 ± 0.12
	16.69	6.072	6.08 ± 0.07
	17.87	6.368	6.26 ± 0.09
Piperidine	6.94	3.100	38.7 ± 3.5
	6.94	2.910	38.9 ± 1.9
	6.77	3.100	40.7 ± 3.0
	6.77	2.886	41.1 ± 1.0
N-Methylcyclohexylamine	18.44	5.62	1.45 ± 0.1
	18.44	4.92	1.47 ± 0.1
	14.08	4.92	1.50 ± 0.1
Triethylcarbinylamine	47.00	15.78	0.0685 ± 0.004
	61.80	15.78	0.0710 ± 0.007
	61.80	17.58	0.0718 ± 0.001
tert-Butylamine	48.46	10.84	0.179 ± 0.01
	35.60	10.84	0.187 ± 0.03
	35.60	12.33	0.197 ± 0.03

[a] Standard deviation obtained from at least seven observations.

(1) For paper X in this series, see G. Glaros and N. H. Cromwell, *J. Org. Chem.*, **36**, 3033 (1971).

(2) The author to whom all correspondence concerning this article should be addressed.

(3) (a) F. G. Bordwell and D. A. Schexnayder, *J. Org. Chem.*, **33**, 3240 (1968); (b) G. Valkanas and E. S. Waight, *J. Chem. Soc.*, 531 (1964); (c) R. H. De Wolfe and W. G. Young, "The Chemistry of Alkenes," Vol. 1, S. Patai, Ed., Wiley, New York, N. Y., 1964, p 681.

(4) (a) N. H. Cromwell and R. P. Rebman, *J. Org. Chem.*, **32**, 3830 (1967); (b) *Tetrahedron Lett.*, No. 52, 4833 (1965).

(5) G. Maury, E.-M. Wu, and N. H. Cromwell, *J. Org. Chem.*, **33**, 1900 (1968).

(6) For a discussion of nucleophilic, bimolecular, concerted reactions involving four or more bonds, see F. G. Bordwell, *Accounts Chem. Res.*, **3**, 281 (1970).

(7) N. H. Cromwell, K. Matsumoto, and A. D. George, *J. Org. Chem.*, **36**, 272 (1971).

overall second-order kinetics, first order in **1a** and in amine. No term of higher order in amine was apparent upon increasing the concentrations of cyclohexylamine relative to that of **1a**.

Samples of a mixture of **1a** and cyclohexylamine in *n*-hexane were analyzed concurrently for **1a** and for bromide ion. The results, in Table II, show that the

Table II

Values of the Second-Order Rate Coefficients k_2 for the Reactions of β-Benzoyl-γ-phenylallyl Halides, $PhCH{=}C(CH_2X)COPh$, with Amines in *n*-Hexane[a]

X	Amine	Temp, °C	10^3[amine]	10^3[allyl halide]	10^2k_2, l. mol^{-1} sec^{-1}
Br	Cyclohexylamine	41.35	14.87	4.956	2.94
		36.07	14.23	5.260	2.39
		36.07	14.23	4.453	2.31
		31.50	11.09	6.403	1.74[b]
		31.50	11.09	6.403	1.62[c]
		31.50	17.26	5.334	1.75
		31.50	17.26	5.700	1.93
		31.50	19.86	6.476	1.81
		18.40	22.74	6.955	0.60
		18.40	11.37	6.310	0.64
Br	Triethylcarbinylamine	52.50	24.28	8.33	0.304
		41.35	35.45	12.94	0.168
		36.07	31.61	11.50	0.138
		36.07	31.61	15.06	0.137
		31.50	43.50	22.30	0.0802[b]
		31.50	41.10	20.90	0.0942
		31.50	50.67	25.26	0.108
		31.50	50.67	18.15	0.104
Cl	Cyclohexylamine	18.50	22.74	15.61	0.173
		18.50	45.48	15.61	0.166
Cl	Triethylcarbinylamine	25.0	41.47	10.47	0.0122

[a] Rates were measured by the Volhard method for bromide ion unless indicated otherwise. [b] Estimated spectrophotometrically. [c] Estimated concurrently with the preceding rate constant and not included in Table III.

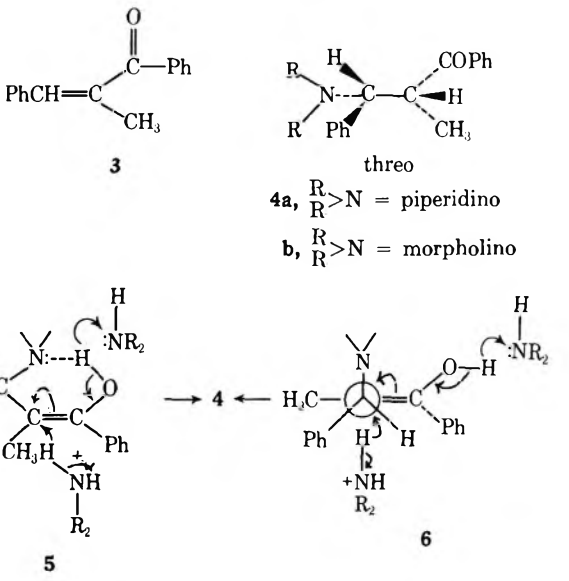
rates estimated by each method were equivalent within experimental error. Similarly, for the reaction of **1a** with triethylcarbinylamine, the spectrophotometric rate constant was approximately equivalent to the volumetric rate constant. Data obtained by the volumetric method gave better correlation over 80–90% of the reaction in a second-order rate plot than the spectroscopic data; hence the volumetric method was preferred.

The effect of varying the leaving groups was examined by comparing the reactivities of **1a** and of **1b** toward cyclohexylamine and triethylcarbinylamine. These results are also presented in Table II.

Activation parameters for the reactions of **1a** with cyclohexylamine and with triethylcarbinylamine were determined and the relevant data are given in Tables II and III.

1-Phenyl-2-benzoylpropene (**3**), an analog of **1a** and **1b** which contains no leaving group, underwent reaction with morpholine and with piperidine *via* a slow 1,4 addition to give the corresponding 2-benzoyl-1-amino-1-phenylpropane, **4a** or **4b**, as indicated in Scheme I. However, 1,4-addition products could not be detected upon similar treatment of **3** with either cyclohexylamine or *tert*-butylamine. The application of either of two models for steric control of asymmetric induction in the reactions between **3** and the secondary

Scheme I



amines predicts the formation of the threo configuration, as represented in Scheme I. A large vicinal coupling (J = 11 Hz) was observed for protons attached to the adjacent asymmetric centers, suggesting that the conformer in solution contains true trans protons.[8]

Discussion

Three of a number of rate-controlling factors to be considered in nucleophilic substitution reactions are the polarizability and size of the nucleophile and the strength of the new bond between carbon and the nucleophilic atom.[9] The new bond strength is generally proportional to the basicity of the nucleophile toward a proton and, if this parameter is overall rate limiting, we may expect the order of nucleophilicity to parallel that of the basicity.[9]

We observed the following order of nucleophilicity toward **1a**: piperidine > morpholine > *N*-methylcyclohexylamine ~ cyclohexylamine > *tert*-butylamine > triethylcarbinylamine.

The basicities of four of the amines may be written: piperidine > *tert*-butylamine > cyclohexylamine > morpholine.[10] This order is not in agreement with our observed order of nucleophilicity, indicating that the strength of the developing carbon-nitrogen bond is not overall rate controlling. The rate ratio $k(Et_3CNH_2):k(C_6H_{11}NH_2)$ is approximately 0.054 and is indicative of a considerable decrease in reactivity for the reaction with triethylcarbinylamine which originates in a less favorable entropy of activation term, consistent with a more compressed transition state for reaction with the more bulky amine.

N-Methylcyclohexylamine exhibits a slight but real increase in reactivity relative to cyclohexylamine (by a factor of 1.08). It would appear that favorable electron release from the methyl group is of greater importance in controlling the rate than the steric

(8) For a related study, see C. A. Kingsbury and D. C. Best, *J. Org. Chem.*, **32**, 6 (1967).

(9) (a) J. Miller, "Aromatic Nucleophilic Substitution," Elsevier, Amsterdam, 1968, Chapter VI. (b) R. F. Hudson, "Structure and Mechanism in Organophosphorus Chemistry," Organic Chemistry Monographs, Vol. 6, A. T. Blomquist, Ed., Academic Press, London, 1965, Chapter 4.

(10) J. J. Christensen, R. M. Izatt, D. P. Wrathall, and L. D. Hansen, *J. Chem. Soc. A*, 1212 (1969).

TABLE III

ACTIVATION DATA[a] FOR THE REACTIONS OF β-BENZOYL-γ-PHENYLALLYL BROMIDE WITH AMINES IN *n*-HEXANE

Amine	10^2k_2,[b] l. mol^{-1} sec^{-1} 21.5°	21.9°	25°	31.5°	36.07°	41.35°	52.5°	$E^{\ddagger}$, kcal mol^{-1}	10^5A, sec^{-1}
Cyclohexylamine	0.996	1.09	1.28	1.83	2.35	2.94		9.8	1.88
Triethylcarbinylamine			0.0704	0.102	0.138	0.168	0.304	10.3	0.171

[a] $k_2 = Ae^{-E^{\ddagger}/RT}$. [b] From Tables I and II, using arithmetical mean values where appropriate.

requirement of the secondary amine. Piperidine is the most reactive of the amines studied and this result is in agreement with reports by others of facile abnormal substitutions employing piperidine as a nucleophile.[3a]

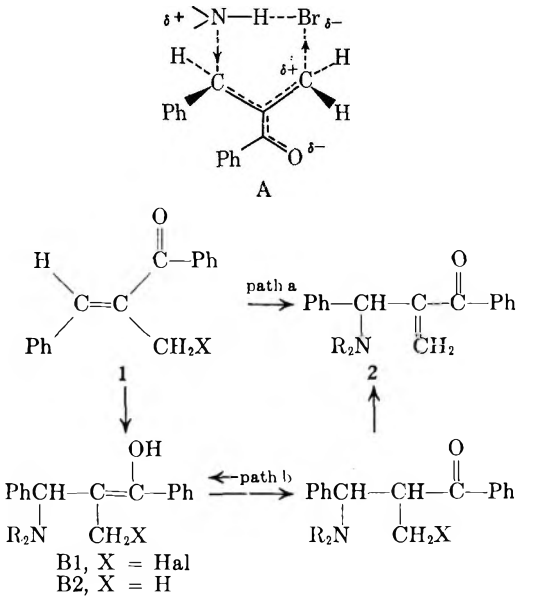
Thus in abnormal substitution reactions with **1a** the relative reactivities of the secondary amines, piperidine and morpholine, which are about equal in size, parallel the order of their basicities (or polarizabilities), whereas the rate data for the primary amines are indicative of a decrease in reactivity with an increase in substitution at the α-carbon atom of the amine.

The ratios of the reactivities of **1a** and **1b**, k(**1a**):k(**1b**), with cyclohexylamine and with triethylcarbinylamine were approximately 3.6 and 5.7, respectively. The leaving group effects of bromine *vs.* chlorine for SN2 reactions show a reactivity ratio of about 50.[11] It is generally accepted that extensive bond breakage occurs in the transition state of an SN2 reaction; thus it would appear that there is only a small extension of the carbon–halogen bond in a rate-limiting transition state for the reactions of **1a** and **1b** with amines. The somewhat greater leaving group ratio with the more polarizable amine is reminiscent of similar effects which have been observed in nucleophilic substitutions at aromatic carbon atoms.[12]

Two main pathways can be envisaged for the reactions of compounds **1a** and **1b** with primary and secondary amines in *n*-hexane and are presented in Scheme II. In path a, we consider that, as the amine approaches the sp^2-hybridized γ-carbon atom, the carbonyl group oxygen accepts much of the developing negative charge resulting in a transition state with structure A, in which there is only a little carbon–halogen bond extension. The approach of the amine could be aided by hydrogen bonding either with the carbonyl oxygen atom, in a manner similar to that proposed for the reactions of amines with α-bromo ketones,[13] or with the halogen atom, resulting in a cis orientation of the amine and the halogen. A cis orientation of the nucleophile and the leaving group was proven for the abnormal substitution reactions of *trans*-6-alkyl-2-cyclohexenyl-2,6-dichlorobenzoates with piperidine,[14] and it is possible that crowding in a similar transition state, A, may explain the lower reactivities of the bulky primary amines in the present work. Alternatively, the steric retardation may originate from an interaction between substituents at the α-carbon atom of the amine and the γ-phenyl ring.

Path b would involve a 1,4 addition of the amine to the α,β-unsaturated ketone grouping of **1** to give an

SCHEME II



intermediate B, followed by an E2 elimination of hydrogen halide. We would expect the energetics for the formation of B1, with X = Hal, and B2, with X = H, to be similar, and for the formation of B1 to be rate limiting in the absence of any amine catalysis. However, the chalcone, **3**, reacted at an extremely slow rate with amines, and it therefore seems reasonable that the formation of **2** does not proceed *via* this addition–elimination mechanism.

Experimental Section[15]

2-[α-*N*-Methylcyclohexylamino)benzyl]acrylophenone (2a).—*N*-Methylcyclohexylamine (2.25 g, 0.02 mol) and **1a** (3.0 g, 0.01 mol) in 200 ml of *n*-hexane were stirred for 66 hr at room temperature. A ^{1}H nmr spectrum of the crude products indicated an absence of **1** and the presence of **2c** and **3c** in a 1:1 ratio.

N-Methylcyclohexylamine (1.95 g, 0.017 mol) in 100 ml of *n*-hexane was added dropwise over a period of 24 hr to a stirred solution of **1** (3.0 g, 0.01 mol) at *ca.* 25°; 2.60 g (91%) of **2a** was obtained. Recrystallization from *n*-pentane resulted in long, colorless needles: mp 67–67.5°; $\nu_{C=O}$ (CCl_4) 1656 cm^{-1}; nmr (CCl_4) *ca.* 455 (m, 10 H, aromatic), 378 (t, 1 H, J = 1.2 Hz, vinyl), 352 (t, 1 H, J = 1.2 Hz, vinyl), 310 (s, 1 H, benzyl), 235 (s, 3 H, methyl), and 120–160 Hz (m, 11 H, cyclohexyl).

Anal.[15b] Calcd for $C_{23}H_{27}NO$: C, 82.84; H, 8.17; N, 4.20. Found: C, 82.91; H, 8.16; N, 4.35.

Reaction of β-Benzoyl-γ-phenylallyl Chloride (1b) with Cyclohexylamine.—Cyclohexylamine (0.20 g, 0.002 mol) was added to **1b** (0.26 g, 0.001 mol) in 50 ml of *n*-hexane. The mixture was stirred at room temperature for 4 hr and filtered, and the filtrate evaporated to a white solid. A pmr spectrum of the solid in

(11) A. Streitwieser, Jr., "Solvolytic Displacement Reactions," McGraw-Hill, New York, N. Y., 1962, p 30.

(12) J. F. Bunnett, *J. Amer. Chem. Soc.*, **79**, 5969 (1957).

(13) (a) P. L. Southwick and R. J. Shozda, *ibid.*, **81**, 5435 (1959); (b) N. H. Cromwell and D. J. Cram, *ibid.*, **65**, 301 (1943).

(14) G. Stork and W. N. White, *ibid.*, **78**, 4609 (1956).

(15) Melting points were determined by the capillary method with a calibrated thermometer. The infrared spectra were taken on a Perkin-Elmer Model 21 instrument and ultraviolet spectra were obtained with a Cary Model 11 or a Cary Model 14 instrument. The 60-MHz nmr spectra were determined on a Varian A-60 spectrometer and the chemical shifts were recorded relative to internal tetramethylsilane (0.0 Hz). Elemental analyses were performed by either (a) Micro-Tech Laboratories, Ill., or (b) Alfred Bernhardt, West Germany.

carbon tetrachloride indicated only compounds **1b** and **2b** in a ratio of 1:4 by comparison with pmr spectra of authentic samples of **1b** and **2b** in the same solvent.

Reaction of 1b with Triethylcarbinylamine.—Triethylcarbinylamine (2 equiv) and **1b** (1 equiv) in *n*-hexane were stirred at room temperature for 4 days. A pmr spectrum of the hexane-soluble compounds in carbon tetrachloride indicated only compounds **1b** and **2f** by comparison with pmr spectra of authentic samples in the same solvent.

threo-**2-Benzoyl-1-piperidino-1-phenylpropane** (**4a**).—Piperidine (0.95 g, 0.011 mol) was added to 2.22 g (0.010 mol) of 2-benzoyl-1-phenylpropene and the mixture was allowed to react at room temperature for 7 days. The mixture solidified and was crystallized from 100 ml of a 1:1 ethyl ether–methanol mixture. The white solid which separated weighed 2.96 g (96%): mp 141–142°; λ_{max} (isooctane) 240 mμ (ε 13,900); $\nu_{C=O}$ (CCl_4) 1688 cm^{-1}; nmr peaks ($CDCl_3$) 435–480 (m, 5 H, benzoyl), 428 (s, 5 H, phenyl), 230–280 (m, J = 11, 6.5 Hz, 2 H, methines), 120–170 (m, 4 H α to N), 60–120 Hz (β and γ to N and methyl, J = 6.5 Hz).

Anal.[15a] Calcd for $C_{21}H_{25}NO$: C, 82.04; H, 8.20; N, 4.56. Found: C, 81.78; H, 8.29; N, 4.50.

threo-**2-Benzoyl-1-morpholino-1-phenylpropane** (**4b**).—To a 6.66-g (0.030 mol) sample of 2-benzoyl-1-phenylpropene (**7**) was added 2.61 g (0.030 mol) of morpholine and the mixture was allowed to stand at room temperature for 5 days. The mixture was analyzed by nmr spectrometry at various stages of conversion and only one configurational isomer was detected along with starting material. The mixture solidified upon standing and recrystallization of the solid from a 1:1 ethyl ether–methanol mixture yielded 7.24 g (80%) of white crystals: mp 149–150°; λ_{max} (isooctane) 240 mμ (ε 14,100); $\nu_{C=O}$ (CCl_4) 1688 cm^{-1}; nmr peaks 435–480 (m, 5 H, benzoyl), 431 (s, 5 H, phenyl), 230–280 (m, 2 H, J = 11, 6.5 Hz, methines), 210–230 (t, 4 H, J = 5 Hz, α to O), 120–170 (4 H, α to N), and 88 Hz (d, 3 H, J = 6.5 Hz, methyl).

Anal.[15a] Calcd for $C_{20}H_{23}NO_2$: C, 77.64; H, 7.49; N, 4.53. Found: C, 77.43; H, 7.49; N, 4.68.

Materials Used in Kinetic Studies.—β-Benzoyl-γ-phenylallyl bromide (**1a**) and the corresponding chloride (**1b**) were prepared as described previously.[4] Samples of **1a** which were used for kinetics were recrystallized from ether–hexane mixtures, mp 81° (corrected) and λ_{max} 285 mμ (ε 17,100) in *n*-hexane. The purity of **1b** was checked with data recorded previously.[4] Piperidine and cyclohexylamine were distilled from sodium through a 90-cm spinning band. Morpholine, *tert*-butylamine, triethylcarbinylamine, and *N*-methylcyclohexylamine were distilled from barium oxide and redistilled twice. All the compounds used in kinetic studies were purified immediately before use. Fisher Spectroanalyzed *n*-hexane was used as the solvent in the reactions which were monitored by uv spectroscopy. For other kinetic studies Phillip's *n*-hexane was freshly distilled from calcium hydride.

Kinetic Procedures.—The rates of formation of halide ion in the reactions of **1a** and **1b** with amines were obtained by an ampoule technique. The reactions were arrested by cooling to −80° and the contents of the ampoules were extracted into dilute nitric acid. The halide ion content of the aqueous layer was estimated by the Volhard method using a visual end point. The initial concentrations of the amine solutions were estimated by the addition of aliquots to a known excess of hydrochloric acid in methanol and back titration against a standard solution of morpholine in methanol using a pH meter.

The reactions of **1a** and of **1b** with cyclohexylamine and of **1a** with triethylcarbinylamine were also followed by a sampling technique. The rate of disappearance of the band in the 280-mμ region due to the cinnamoyl chromophore of **1a** or **1b** was measured. Absorption in this region due to the products **2b** or **2f** was slight and suitable corrections were made.

The rate constants were evaluated from the following expression, by the method of linear least squares

$$k_2 = \frac{1}{t(a - 2b)} \ln \frac{b(a - 2x)}{a(b - x)}$$

where a and b are the initial concentrations of the amine and allyl halide, respectively, x is the concentration of product, and t is the corresponding time.

Registry No.—**1a**, 14181-92-1; **1b**, 14181-99-8; **2a**, 31893-05-7; **4a**, 31893-06-8; **4b**, 31893-07-9; cyclohexylamine, 108-91-8; morpholine, 110-91-8; piperidine, 110-89-4; *N*-methylcyclohexylamine, 100-60-7; triethylcarbinylamine, 1571-51-3; *tert*-butylamine, 75-64-9.

Acknowledgment.—This work was supported in part by Grant No. 02931 from the National Cancer Institute of the U. S. Public Health Service.

1,2,4-Triazines. VI. Tautomerism in Substituted 2,3-Dihydro-3-oxo-1,2,4-triazines

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Received March 16, 1971

A series of 2,3-dihydro-3-oxo-1,2,4-triazines have been prepared. It has been established that **4c,e** is the major tautomer, where R_1 and/or R_2 = C_6H_5. When the substituent at C-5 is a methyl group, a methyl–methylene (**8b** ⇋ **9b**; **8d** ⇌ **9d**) tautomeric mixture exists. The equilibrium constants for these equilibria were determined.

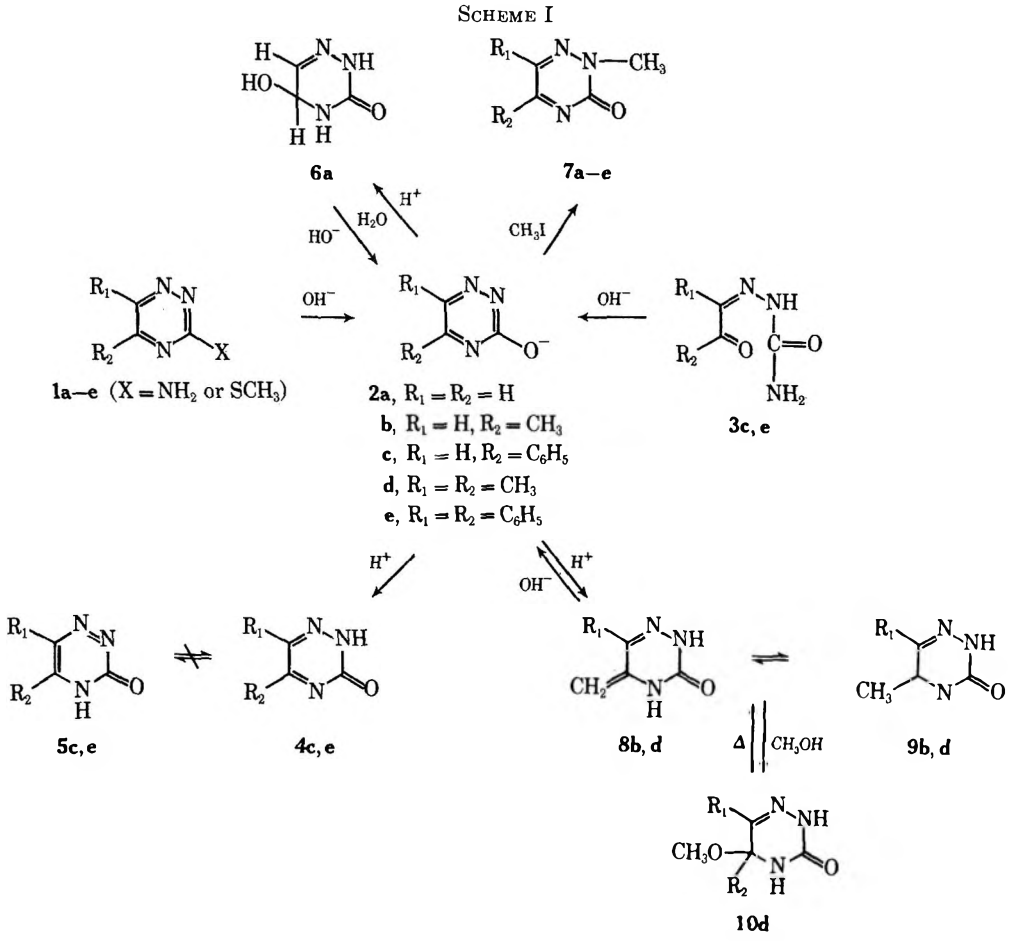
We have for some time[1–4] been interested in 1,2,4-triazines and now wish to describe a study of the tautomeric equilibria of some 2,3-dihydro-3-oxo-1,2,4-triazines. These compounds can in principle be prepared either by hydrolysis of 3-amino- (**1**, X = NH_2) or 3-methylthio (**1**, X = SCH_3) derivatives, or by cyclization of semicarbazone derivatives such as **3** (see Scheme I).

The conversions of compounds **3c–e** to compounds **2c–e**, respectively, have been described in the literature.[5,6] However, in our hands, using the described conditions, no product could be isolated from **3d**. This observation substantiates earlier reports to this effect.[7] Base hydrolysis of either 3-amino- or 3-methylthio-1,2,4-triazines (**1a–e**, X = NH_2 or SCH_3) gives the alkali metal salts of the corresponding 3-hydroxy-1,2,4-triazines (**2a–e**).[8]

Since the chemical shifts of the ring protons and the

(1) W. W. Paudler and J. M. Barton, *J. Org. Chem.*, **31**, 1720 (1966).
(2) W. W. Paudler and T. K. Chen, *J. Heterocycl. Chem.*, **7**, 767 (1970).
(3) W. W. Paudler and T. K. Chen, *J. Org. Chem.*, **36**, 787 (1971).
(4) W. W. Paudler and T. K. Chen, *J. Heterocycl. Chem.*, **4**, 224 (1967).
(5) W. Seibert, *Ber.*, **80**, 494 (1947).
(6) S. Rossi, *Rend. Ist. Lomb. Sci. Lett., Cl. Sci. Mat. Natur.*, **83**, 173 (1955); *Chem. Abstr.*, **50**, 10742h (1956).
(7) C. L. Pitzer, "The Chemistry of 1,2,4-Triazine and Some Related Compounds," Ph.D. Thesis, West Virginia University, 1967.
(8) The statement has been made[7] that basic hydrolysis of 3-amino-1,2,4-triazine (**1a**, X = NH_2) does not lead to identifiable products. This observation is now negated by our results.

SCHEME I



methyl protons in these alkali metal salts are very similar to the chemical shifts of the comparable protons in the 3-methylthio and 3-amino derivatives,[3] one can conclude that the negative charge resides largely on the oxygen atom, as shown in structure 2. By analogy, the 5,6-diphenyl derivative (**2e**) is represented similarly.

On treatment of these salts with dilute acid, the expected oxo compounds (**4**) were obtained only in those instances where a phenyl substituent is present at C_5 (compounds **2c** and **e**).

The position of the tautomeric equilibrium **4** $\rightleftharpoons$ **5** can be established by comparing the uv spectra of the 3-oxo compounds (**4** and **5**) with the spectra of the corresponding N-2 and N-4 methylated derivatives (**7e** and **12e**, respectively).

The condensation of 2-methylsemicarbazide with benzil has been reported[9] to afford the same 2,3-dihydro-3-oxo-1,2,4-triazine (**7e**) as is obtained from the treatment of an alkali metal salt of 5,6-diphenyl-3-hydroxy-1,2,4-triazine with methyl iodide. Thus, the site of N-alkylation is established and one of the reference compounds needed for the uv study is available. The other needed isomer (**12e**) was prepared by condensing benzil with 4-methylsemicarbazide under acidic conditions (Scheme II).

A comparison of the uv spectrum of the nonalkylated derivative (**4e**) with the spectra of the N-2 and N-4 methyl derivatives (**7e** and **12e**) (see Table I) clearly shows that the equilibrium **4e** $\rightleftharpoons$ **5e** lies essentially totally in favor of the N_2H tautomer **4e**. Consequently, it appears that the tautomer possessing a N=N bond (**5e**) is considerably less stable than the one (**4e**) where this structural feature is not present. Whether this conclusion is also valid for those 3-oxo derivatives where C-5 and C-6 are either unsubstituted or have a methyl substituent, cannot be answered because of the complications to be discussed in the next section. However, there seems to be no *a priori* reason to suspect that the 5,6-diphenyl compound would behave substantially different from the other 3-oxo derivatives.

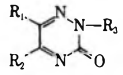
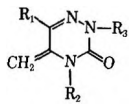
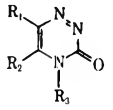
The direct alkylation with methyl iodide of the sodium salts of the other 3-hydroxy-1,2,4-triazines (**2a–d**) yielded the expected N-2 alkylated derivatives in satisfactory yields. That alkylation has indeed occurred at N-2 and not at N-4 is evident from the similarity of the proton chemical shifts of the $N\text{-}CH_3$ groups in all of these compounds, with the proton chemical shifts of the methyl group in the authentic N-2 methyl derivative **2e** (the methyl proton chemical shift in the N-4 methyl compound **12e** is significantly different).

When the sodium salt of 3-hydroxy-1,2,4-trazine (**2a**) is treated with aqueous acid, there is obtained a compound whose molecular formula, $C_3H_5N_3O_2$, differs from the expected one, $C_3H_3N_3O$, by the elements of water. We have already commented on the propensity with which the 1,2,4-triazines undergo convalent hydration across the 4–5 bond,[2] an observation which has recently been confirmed.[10] Consequently, we can

(9) M. Polonovski, M. Pesson, and P. Rajzman, *Bull. Soc. Chim. Fr.*, 240 (1955).

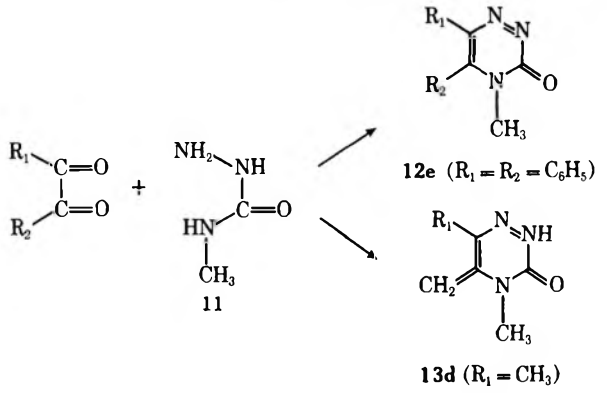
(10) N. Vinot and J.-P. M. Packo, *ibid.*, 12 (1970).

Table I
Uv Spectral Data for Various 1,2,4-Triazin-3-ones[a]

Compd		λ_{max}, mμ ($\epsilon \times 10^3$)	λ_{min}, mμ ($\epsilon \times 10^3$)	Compd no.
	$R_1 = R_3 = H$; $R_2 = CH_3$[b]	300 (2.17) 220 (3.96) sh	258 (0.50)	9b
	$R_1 = R_2 = CH_3$; $R_3 = H$[b]	295 (3.03) 215 (9.14)	253 (0.63)	9d
	$R_1 = R_3 = H$; $R_2 = C_6H_5$	292 (13.28) 222 (11.07)	246 (1.71)	4c
	$R_1 = R_2 = C_6H_5$; $R_3 = H$	335 (4.17) sh 295 (6.55) sh 252 (14.88)	233 (13.39)	4e
	$R_1 = H$; $R_2 = R_3 = CH_3$	303 (2.82)	256 (0.61)	7b
	$R_1 = R_2 = R_3 = CH_3$	308 (2.88) 213 (9.92) sh	248 (0.69)	7d
	$R_1 = H$; $R_2 = C_6H_5$; $R_3 = CH_3$	295 (12.67) 223 (10.89)	248 (1.78)	7c
	$R_1 = R_2 = C_6H_5$; $R_3 = CH_3$	338 (4.97) 290 (6.16) 254 (14.30)	320 (4.77) 233 (11.93)	7e
	$R_1 = R_2 = CH_3$; $R_3 = H$	286 (4.76) 227 (13.89)	252 (1.79)	13d
	$R_1 = R_2 = C_6H_5$; $R_3 = CH_3$	292 (10.72) 230 (10.92) sh 215 (15.43) sh	255 (5.81)	12e

[a] In 95% EtOH. [b] Tautomeric mixture of CH_3– and CH_2= at R_2.

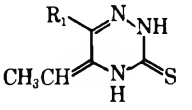
Scheme II



assign structure **6a** to this covalently hydrated species. That we are indeed dealing with this compound is supported by its nmr spectrum, which is composed of an AB proton-on-carbon system (τ_5 4.62, τ_6 2.92, $J_{5,6}$ = 3.0 Hz) which is analogous to those previously described by us[2] as being typical of this type of triazine derivative. All attempts to date (sublimation, heating in toluene in the presence of a Dean–Stark trap) have failed to yield the dehydrated compound **4a**. Treatment with base does, however, regenerate the salt of 3-hydroxy-1,2,4-triazine (**2a**) quantitatively.

The remaining two alkali metal salts (**2b** and **2d**), when treated with aqueous acetic acid, afforded compounds with the expected molecular formulas. However, their nmr spectra are rather unique in that, in addition to the patterns expected for structures **9b** and **9d**, one observes an olefinic AB system (τ_1 5.9, τ_2 5.7, $J_{1,2}$ = 1.0 Hz) as well as the presence of an "additional" methyl peak (τ 8.05) in the case of the 5,6-dimethyl derivative and an "additional" highly deshielded singlet (τ 2.82) in the 5-methyl compound.

Since Adams and Shepherd[11] have recently shown that 5-ethyl derivatives of some 2,3-dihydro-3-thio-1,2,4-triazines exist in the ethylidene form **14**, one



$R_1 = CH_3, C_2H_5$

14

can conclude that the new peaks observed in the nmr spectra of the mono- and dimethyl derivatives of the oxo compounds are due to the methylene forms **8b** and **8d**, respectively. Thus, the equilibria **8b** ⇄ **9b** and **8d** ⇄ **9d** can be written to account for these observations.

The equilibrium constants of these equilibria can conveniently be determined by nmr as well as by ultraviolet spectroscopy. The latter technique would be applicable if one could obtain the uv spectra of the pure isomers (**8** and **9**).

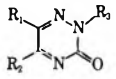
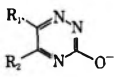
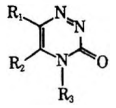
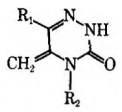
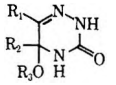
Since the nmr spectra of the N-2 alkylated compounds (**7b** and **7d**) are devoid of any methylene protons, we can assume that these substances exist, at least to the extent of 95%, in the methyl forms (**7b** and **7d**).

On the other hand, when biacetyl is condensed with 4-methylsemicarbazide (**11**), the N-4 methyl derivative **13d** that is obtained exists exclusively in the methylene form (Scheme II and Table II). Thus, the

(11) J. Adams and R. G. Shepherd, *Tetrahedron Lett.*, 2747 (1968).

TABLE II

NMR SPECTRAL DATA FOR SOME 1,2,4-TRIAZINES

Compd		Chemical shifts, τ					Solvent	$J_{1,2}$, cps	Compd no.
		R_1	R_2	R_3	CH_2=	C_6H_5			
	$R_1 = R_3 = H$; $R_2 = CH_3$[a]	2.07	7.62				DMSO		9b
	$R_1 = H$; $R_2 = R_3 = CH_3$	2.32	7.55	6.24			$CDCl_3$		7b
	$R_1 = R_2 = CH_3$; $R_3 = H$[b]	7.60	7.74				DMSO		9d
	$R_1 = R_2 = R_3 = CH_3$	7.55	7.68	6.28			$CDCl_3$		7d
	$R_1 = R_3 = H$; $R_2 = C_6H_5$[c]	1.22				(1.77, 2.36)	DMSO		4c
	$R_1 = H$; $R_2 = C_6H_5$; $R_3 = CH_3$[c]	1.71		6.17		(1.89, 2.50)	$CDCl_3$		7c
	$R_1 = R_2 = C_6H_5$; $R_3 = CH_3$[c]			6.10		(2.62)	$CDCl_3$		7e
	$R_1 = R_2 = C_6H_5$; $R_3 = H$[c]					2.38	DMSO		4e
	$R_1 = R_2 = H$	1.64	1.72				D_2O		2[a]
	$R_1 = H$; $R_2 = CH_3$	1.73	7.64				D_2O		2b
	$R_1 = R_2 = CH_3$	7.66	7.69				D_2O		2d
	$R_1 = R_2 = C_6H_5$; $R_3 = CH_3$[c]			7.03		(3.38)	$CDCl_3$		12e
	$R_1 = R_2 = H$[a]	2.82			5.88 5.80		DMSO	1.0	8b
	$R_1 = CH_3$; $R_2 = H$[b]	8.05			5.88 5.72		DMSO	1.0	8d
	$R_1 = R_2 = CH_3$	7.94	6.90		5.79 5.66		$CDCl_3$	2.0	13d
		7.98	6.98		5.69 5.59		DMSO	2.0	
	$R_1 = R_2 = R_3 = H$	2.92	4.62				D_2O	3.0	6a
	$R_1 = R_2 = R_3 = CH_3$	8.57	8.14	7.06			DMSO		10d

[a] These values represent data taken from the equilibrium mixture of the $CH_3 \rightleftarrows CH_2$= tautomeric mixture of the 3-oxo-2,3-dihydro-5-methyl-1,2,4-triazine. The two species are present in the relative amounts indicated in the text. [b] These values represent data taken from the equilibrium mixture of the 3-oxo-2,3-dihydro-5,6-dimethyl-1,2,4-triazine. The two species are present in the relative amounts indicated in the text. [c] Chemical shift of middle point, indicated by parentheses.

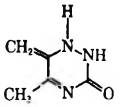
means of establishing the equilibrium constant for the system **8d** ⇄ **9d** by ultraviolet spectroscopy is now available.[12] The equilibrium constant for this equilibrium, determined in 95% ethanol, is 0.71, with the methylene tautomer (**8d**) being the minor component. This value compares well with the equilibrium constant (0.83) determined in DMSO by means of nmr.[13]

An analysis of the nmr spectrum of the equilibrium **8b** ⇄ **9b** in DMSO gives a value of 0.20 for the 5-methyl isomer (**9b**), with the methylene form (**8b**) again being the minor component.

When the 5,6-dimethyl mixture (**8d** ⇄ **9d**) is heated in methanol, one obtains compound **10d**, resulting from addition of 1 mol of methanol across the N_4–C_5 bond in compound **9d**. The nmr spectrum (Table II) and elemental analysis of this compound confirm its structure. Interestingly when this compound is sublimed, it readily reverts to the 3-oxo mixture **8d** ⇄ **9d**. This is in contrast to the stability of the covalently hydrated 2,3-dihydro-3-oxo-1,2,4-triazine (**6a**).

(12) We must, of course, assume that the ultraviolet spectrum of **8** and of **9** is not altered by N-alkylation.

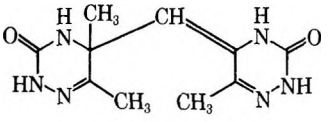
(13) The possibility that the methylene tautomer of the 5,6-dimethyl compound **9d** has the structure i can be eliminated, since the chemical shifts



i

of the methylene protons would be different from those in the 5-methylene cases **8b** and **8d**.

Adams and Shepherd[11] have suggested that 5,6-dimethyl-2,3-dihydro-3-oxo-1,2,4-triazine (**9d**) exists as the dimer **15**.



15

We have found that this dimer is only present in "aged" (2–3 days) and totally absent in freshly prepared solutions. The monomers (**8d** ⇄ **9d**) can be regenerated from the dimer by making an aqueous solution basic and reacidifying it, or by simply subliming it.

Experimental Section

Pmr spectra were obtained, as dilute (5% w/v) solutions in the solvents indicated, with a Varian HA-100 spectrometer. Elemental analyses were done by Mrs. V. Gindelsberger of this department. Mass spectra were obtained on all compounds with a Hitachi Perkin-Elmer RMU-6E mass spectrometer, with an ionization potential of 80 eV. Melting points are corrected.

General Procedure A. Base Hydrolyses of 3-Amino- or 3-Methylthio-1,2,4-triazines.—A solution of the appropriate 3-amino- (**1a–e**, X = NH_2)[14] or 3-methylthio- (**1a–e**, X = SCH_3)[3] 1,2,4-triazine (0.4 mol) in 200 ml of water containing 30 g (0.75 mol) of potassium hydroxide was heated with stirring for 3 hr at 50–60°.

The reaction mixture was then evaporated to dryness under vacuum and the remaining solid was recrystallized from methanol

(14) J. Saikawa and T. Maeda, *Yakugaku Zasshi*, **87**, 1501 (1967), and references cited therein.

to yield the potassium salt of the appropriate 2,3-dihydro-3-oxo-1,2,4-triazine (2a–e) (see Table III for analytical data). This salt was then dissolved in a minimum amount of water and the solution was carefully neutralized by the dropwise addition of acetic acid. The precipitate was collected, and recrystallized from 95% ethanol, and the resulting material was further purified by sublimation (see Table III for analytical data).

Table III
Analytical Data for Various 1,2,4-Triazines[a]

Compd, molecular formula (no.)	Mp, °C	Sublimation temp (at 0.2 mm), °C	Yield, %	Procedure
$C_4H_5N_3O$ (9b)	142	120	56.8	A
$C_5H_7N_3O$ (9d)	224	162	72	A
$C_9H_7N_3O$ (4c)	240	162	75	A
$C_{15}H_{11}N_3O$ (4e)	245	160	68	A
$C_4H_5N_3O$ (7a)	77.5	70	87	B
$C_5H_7N_3O$ (7b)	138	50	<10	B
$C_6H_9N_3O$ (7d)	86	72	82	B
$C_{10}H_9N_3O$ (7c)	158.5	98	79	B
$C_{16}H_{13}N_3O$ (7e)	152	98	72	B
$C_{15}H_{13}N_3O$ (12e)	181	115	<10	C
$C_6H_9N_3O$ (13d)	154	80	75	C
$C_3H_2N_3OK$ (2a)	262–265		23	A
$C_3H_5N_3O_2$ (6a)	320 dec		50 from 18	A
$C_6H_{11}N_3O_2$ (10d)	219		74	D

[a] Satisfactory analytical values (±0.3% for C, H, N) were recorded for all compounds in table: Ed.

The 2,3-dihydro-3-oxo-1,2,4-triazine (4a) could not be isolated by the above process but was obtained as its crystalline covalently hydrated derivative 6a by addition of acetic acid to an aqueous solution of its potassium salt (2a) (see Table III).

General Procedure B. Direct Alkylation of 2,3-Dihydro-3-oxo-1,2,4-triazines.—A solution of 1 mmol of either the alkali metal salt or the "free" 3-oxo compound obtained from procedure A, in 20 ml of methanol containing 1 mmol of $NaOCH_3$ was vigorously stirred with 5 mmol of CH_3I. After 40 hr, the reaction mixture was evaporated to dryness and the residue was extracted with three 50-ml portions of $CHCl_3$. The dried (anhydrous Na_2CO_3) $CHCl_3$ extracts were evaporated and the residue was sublimed to afford the 2-methyl derivatives of the corresponding 3-oxo compounds (7a–e) (see Table III for the appropriate analytical data).

General Procedure C. Syntheses of 3,4-Dihydro-4-methyl-3-oxo-1,2,4-triazines.—4-Methylsemicarbazone (4 mmol) is treated at room temperature with the appropriate α,β-dicarbonyl compound dissolved in 25 ml of ethanol. The precipitate which formed was collected after 15 min and dissolved in 10 ml of acetic acid. The solution was heated under reflux for 3 hr and evaporated to dryness, and the remaining solid was sublimed at the temperatures indicated in Table III.

Formation of 5,6-Dimethyl-4-methoxy-3-oxo-2,3,4,5-tetrahydro-1,2,4-triazine (10d) (Procedure D).—A solution of 2,3-dihydro-5,6-dimethyl-3-oxo-1,2,4-triazine (25 mg, 0.2 mmol) was heated in 2 ml of methanol for 3 hr. After concentrating the solution to about 0.5 ml, it was allowed to cool to room temperature to yield 20 mg of compound 10d (see Table III for analytical data).

Registry No.—2a, 31952-58-6; 2b, 31952-59-7; 2d, 31952-60-0; 4c, 31952-61-1; 4e, 4512-00-9; 6a, 31952-63-3; 7a, 31952-64-4; 7b, 31947-27-0; 7c, 31947-28-1; 7d, 31999-38-9; 7e, 18510-97-9; 8b, 31947-30-5; 8d, 31947-31-6; 9b, 31947-32-7; 9d, 31947-33-8; 10d, 31947-35-0; 12e, 31947-34-9; 13d, 31947-36-1.

Acknowledgment.—We wish to thank the Donors of the Petroleum Research Fund, administered by the American Chemical Society, for generous support of this work.

Preparation of 6-Substituted Pterins *via* the Isay Reaction

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Received May 18, 1971

Various 6-substituted pterins have been prepared by a modification of the Isay reaction. When the condensation of either methyl glyoxal or phenyl glyoxal with 2,4,5-triamino-4-hydroxypyrimidine was carried out in the presence of 2-mercaptoethanol, mixtures of 6- and 7-substituted pterins were obtained with the 6 isomer predominant. The pure 6-methyl- and 6-phenylpterins were obtained from the mixture of isomers by crystallization from alkaline solution.

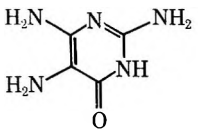
The Isay reaction is the original method for obtaining pteridines from the condensation of aminopyrimidines and α,β-diketo compounds.[2] We report here our success in using this reaction with α-keto aldehydes to produce 6-substituted 2-amino-4-hydroxypteridines (pterins). This route to pterins, not symmetrically substituted in the 6 and 7 position, has not been very satisfactory in the past for two reasons. The direction of condensation was seldom entirely in one direction, normally with the less desirable 7 isomer predominating. Second, the separation of the resulting mixture of 6 and 7 isomers was extremely difficult.

The ready availability of these compounds is of considerable interest because of their analogy to dihydrofolate[3] and their participation in the tetrahydro form in aromatic hydroxylations.[4,5]

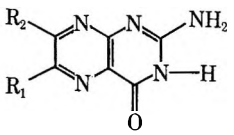
Numerous attempts have been made to direct the Isay condensation in the direction of the 6 isomer. Forrest and Walker[6] examined the effect of hydrazine hydrate on the condensation of both acetol and methyl glyoxal with 2,4,5-triamino-6-hydroxypyrimidine (1). Although the effect was in the desired direction, the yields were low. Sodium bisulfite and strong acid

(1) Author to whom inquiries should be addressed.
(2) A. Albert, *Quart. Rev., Chem. Soc.*, **6**, 197 (1952).
(3) J. M. Whiteley and F. M. Huennekins, *Biochemistry*, **6**, 2620 (1967).
(4) S. Kaufman, *Annu. Rev. Biochem.*, **36**, 171 (1967).
(5) C. B. Storm and S. Kaufman, *Biochem. Biophys. Res. Commun.*, **32**, 788 (1968).
(6) H. S. Forrest and J. Walker, *J. Chem. Soc.*, 2077 (1949).

have also been used.[2,7] The results reported by Semb[7] using sodium bisulfite in the preparation of **2c** are similar to those reported here, although his yields are much lower. Angier[8] observed that the condensation of phenylglyoxal diethyl acetal led to a good yield of 2-amino-4-hydroxy-6-phenylpteridine (**2a**). Baugh and Shaw[9] used cysteine as an antioxidant to protect **1** from self-condensation in the reaction of **1** with dihydroxyacetone to give **2e**. Since the cysteine was present in a much smaller amount than the carbonyl compound, it is unlikely that a directive effect such as reported here was operating. We have observed that



1



2a, $R_1 = C_6H_5$; $R_2 = H$
b, $R_1 = H$; $R_2 = C_6H_5$
c, $R_1 = CH_3$; $R_2 = H$
d, $R_1 = H$; $R_2 = CH_3$
e, $R_1 = CH_2OH$; $R_2 = H$

methyl glyoxal and phenyl glyoxal will condense with **1** under mild basic conditions in the presence of 2-mercaptoethanol to give **2c** and **2a** as the predominant isomers. Furthermore, the pure 6 isomers may be obtained by simple crystallization from base. By analogy to Angier's results, we believe the reactive intermediate to be the thiohemiacetal of the diketo compound. An even more direct route to **2a** is to simply carry out the condensation of the phenyl glyoxal and **1** at pH 4. Under these conditions pure **2a** is obtained. At pH 8 pure 2b is obtained; at intermediate pH a mixture of isomers is obtained. It is interesting to note that the directive effects of the mercaptoethanol are in the opposite sense of the directive effects of pH on this condensation. In other instances when one has acid or base sensitive functional groups in the α-keto aldehyde, the direction of condensation may be controlled in either acidic or basic solution. This is illustrated by the preparation of **2c** and **2d** under identical conditions of pH.

Analysis of mixtures of pterin isomers has also been a problem in the past. The most satisfactory method to date has been that of Petering and Schmitt.[10] They demonstrated that the isomer content of crude mixtures of 2-amino-4-hydroxy-6- (and 7-) alkylpteridines can be determined by measuring the ratio of the absorbances at two specific wavelengths in the ultraviolet region of the absorption spectrum. Pmr studies of pterins in trifluoroacetic acid solution did not reveal[11] any difference in the chemical shift of the vinyl protons in the pterin isomers. We have observed the pmr spectra of these compounds under basic conditions and in all cases the vinyl protons in the different isomers are separated by 0.1 ppm or more and the isomer ratios are easily determined by proton integration. This technique is not susceptible to interference by colored side products and is more accurate for assaying crude mixtures than the ultraviolet-peak ratio technique. The activity of **2c** and **2d**, after reduction to the tetrahydro form, as cofactors in the enzymatic hydroxylation of phenylalanine to tyrosine have been discussed earlier by Storm and Kaufman.[5]

(7) J. Semb, U. S. Patent 2,477,426; *Chem. Abstr.*, **44**, 1146c (1950).
(8) R. B. Angier, *J. Org. Chem.*, **28**, 1398 (1963).
(9) C. M. Baugh and E. Shaw, *ibid.*, **29**, 3610 (1964).
(10) H. G. Petering and J. A. Schmitt, *J. Amer. Chem. Soc.*, **71**, 3977 (1949).
(11) A. Dieffenbacher, R. Mondelli, and W. V. Phillipsborn, *Helv. Chim. Acta*, **49**, 1355 (1966).

Experimental Section

Methods.—Absorption spectra were obtained with a Cary Model 14 recording spectrophotometer. Proton magnetic resonance spectra were determined with a Varian A-60 spectrometer using sodium 2,2-dimethyl-2-silapentanesulfonate (DDS) as an internal standard. Chemical shifts are reported as δ values in parts per million with DDS = 0 ppm. The results are reported in Table I.

TABLE I
PROTON RESONANCE DATA ON PTERIDINES[a]

Compd	Vinyl proton	Methyl group	Phenyl group
2a	8.50		(*m*, *p*) 7.22; (*o*) 7.39
2b	8.39		(*m*, *p*) 7.39; (*o*) 7.49
2c	8.45	2.55	
2d	8.16	2.52	

[a] Pmr spectra were run at 0.20 *M* concentration in 1 *M* NaOD. Chemical shifts are reported in parts per million relative to DDS internal standard with DDS = 0 ppm.

Materials.—Chemicals were obtained from the following sources: 2,4,5-triamino-6-hydroxypyrimidine sulfate from K and K Laboratories; methyl glyoxal (pyruvaldehyde) obtained as the 40% aqueous solution from Aldrich; phenyl glyoxal from Pierce Chemical Co.

2-Amino-4-hydroxy-6-methylpteridine.—2,4,5-Triamino-6-hydroxypyrimidine sulfate (10 g, 42 mmol) was suspended in 100 ml of water and 10 g (42 mmol) of $BaCl_2 \cdot 2H_2O$ was added and the solution was stirred for 10 min. The $BaSO_4$ was removed by vacuum filtration on a Büchner funnel, 1 ml of 2-mercaptoethanol was added, and the pyrimidine solution was neutralized with excess $NaHCO_3$. Aqueous 40% pyruvaldehyde (7.56 g, 42 mmol) was diluted with 50 ml of H_2O, 10 g (126 mmol) of 2-mercaptoethanol was added, and the solution was neutralized with excess $NaHCO_3$. The solutions were combined, heated on a steam bath for 30 min, brought to pH 7 with acetic acid, and placed in the cold overnight. The precipitate was filtered, washed with water and then acetone, and dried under high vacuum (7.3 g, 41 mmol, 98%). This material consisted of 75% 6 isomer and 25% 7 isomer by pmr proton integration.

The above isomer mixture (4.5 g) was dissolved in 90 ml of 1 *M* sodium hydroxide with heating, and the solution was filtered and placed in the cold overnight. The sodium salt of **2c** was collected by vacuum filtration. The sodium salt was dissolved in a minimum amount of water, the solution was brought to pH 7.0 with acetic acid, and the precipitate was collected by vacuum filtration. The precipitate was washed successively with cold water, acetone, and ether and finally dried at high vacuum (2.4 g, 53%): λ_{max} (0.1 *N* KOH), 251 mμ (ϵ 1.94 $\times$ 10^4), 362 (6.30 $\times$ 10^3). *Anal.* Calcd for $C_7H_7N_5O$: C, 47.5; H, 3.95; N, 39.5. Found: C, 47.2; H, 4.09; N, 39.8.

2-Amino-4-hydroxy-7-methylpteridine.—2,4,5-Triamino-6-hydroxypyrimidine sulfate (4.0 g, 16.8 mmol) was suspended in 80 ml of H_2O, and $BaCl_2 \cdot 2H_2O$ (4.0 g, 16.8 mmol) was added. The solution was stirred for 10 min and filtered. The filtrate was neutralized with excess $NaHCO_3$. Aqueous 40% pyruvaldehyde (3.5 g, 16.8 mmol) was added to the pyrimidine solution, and the mixture was heated on the steam bath for 30 min and allowed to stand overnight in the cold. The solution was then brought to pH 7 with acetic acid and the precipitate was collected by vacuum filtration. The filter cake was washed with water and then acetone. This material showed no 2c isomer by pmr analysis. The filter cake was then dissolved in 135 ml of warm 0.1 *M* potassium hydroxide, the solution was passed over a 4 $\times$ 2 cm bed of triethylaminoethyl cellulose on a glass funnel, and the solution was brought to pH 7.0 with acetic acid. The precipitate was collected by vacuum filtration, washed with water

and then acetone, and dried under high vacuum (2 g, 11.3 mmol, 67%): λ_{max} (0.1 *N* KOH) 250 mμ (ε 1.72 × 10⁴), 354 (7.17 × 10³). *Anal.* Calcd for $C_7H_7N_5O$: C, 47.5; H, 3.95; N, 39.5. Found: C, 47.3; H, 4.08; N, 39.9.

2-Amino-4-hydroxy-6-phenylpteridine.—2,4,5-Triamino-6-hydroxypyrimidine sulfate (2.0 g, 8.4 mmol) was suspended in 30 ml of H_2O, and $BaCl_2 \cdot 2H_2O$ (2.0 g, 8.4 mmol) was added. The solution was stirred for 10 min and filtered. The filtrate was adjusted to a pH of 4.0 with sodium acetate. Phenyl glyoxal (1.1 g, 8.2 mmol) was dissolved in 10 ml of methanol and added to the pyrimidine solution. The resulting mixture was heated on the steam bath for 3 hr. The pale yellow precipitate was collected on a sintered-glass filter and washed with water. This material, pure **2a** by pmr analysis, was dissolved in a minimum amount of 1 *M* sodium hydroxide and the sodium salt was precipitated with 10 *M* sodium hydroxide. The sodium salt was dissolved in a minimum amount of hot 1 *M* sodium hydroxide and cooled overnight. This pale yellow material was taken up in water and the solution was brought to neutrality with acetic acid. The pale yellow precipitate was collected by vacuum filtration, washed with water and acetone, and dried at high vacuum (0.85 g, 3.5 mmol, 41%): λ_{max} (0.1 *M* NaOH) 270 mμ (ε 2.38 × 10⁴), 377 (1.00 × 10⁴). *Anal.* Calcd for $C_{12}H_9N_5O$: C, 60.3; H, 3.8; N, 29.3. Found: C, 60.0; H, 3.9; N, 29.6.

2-Amino-4-hydroxy-7-phenylpteridine.—2,4,5-Triamino-6-hydroxypyrimidine (4 g, 16.8 mmol) was suspended in 60 ml of H_2O, and $BaCl_2 \cdot 2H_2O$ (4 g, 16.8 mmol) was added. The solution was stirred for 10 min and filtered. The pH of the filtrate was adjusted to 9.0 with 1 *M* sodium hydroxide. Phenyl glyoxal (2.2 g, 16.4 mmol) in 20 ml of methanol was added slowly, and the pH of the solution was kept above 8 with 1 *M* sodium hydroxide. The solution was stirred for 2 hr at room temperature and the pH was adjusted to neutrality with acetic acid. The precipitate was collected by vacuum filtration and washed with water and acetone. This material was pure **2b** by pmr analysis. The filter cake was suspended in 100 ml of hot dimethylformamide and concentrated hydrochloric acid was added until all the material dissolved. The solution was allowed to cool to room temperature and placed in the cold overnight. The crystals were collected by vacuum filtration and taken up in water, the pH was adjusted to neutrality, and the precipitate was collected by vacuum filtration and washed with water and acetone (1.60 g, 6.8 mmol, 41%): λ_{max} (0.1 *M* NaOH) 236 mμ (ε 1.97 × 10⁴), 265 (2.00 × 10⁴), 374 (1.28 × 10⁴). *Anal.* Calcd for $C_{12}H_9N_5O$: C, 60.3; H, 3.8; N, 29.3. Found: C, 59.9; H, 3.9; N, 29.5.

Registry No.—**2a**, 25846-86-0; **2b**, 32136-35-9; **2c**, 13165-98-5; **2d**, 13040-58-9.

Novel Imidazole Ring Formation from α Olefins, Carbon Monoxide, and Ammonia

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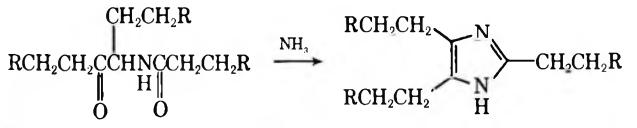
Received June 11, 1971

Rhodium-catalyzed reactions of α olefins with carbon monoxide and concentrated aqueous ammonia give 2,4,5-trialkylimidazoles in one step and in 50–60% yields. When dilute aqueous ammonia was used, an *N*-acyl α-amino ketone intermediate was isolated.

Usually the synthesis of imidazole derivatives requires many complicated steps.[1] We now wish to describe a novel method for obtaining 2,4,5-trialkylimidazoles from α olefins, carbon monoxide, and ammonia in one step. In a typical experiment a suspension of rhodium oxide was heated with ethylene, carbon monoxide, and ammonia at 150° for several hours. From the reaction mixture, 2,4,5-triethylimidazole and propionamide were obtained in 52 and 15% yields, respectively.

When a dilute ammonia solution is used in the reaction of ethylene with carbon monoxide, *N*-propionyl-3-amino-4-hexanone was obtained in 40% yield in addition to a small amount of triethylimidazole. The formation of the amino ketone was confirmed by ir, mass spectra, nmr (three ethyl groups and a methine proton, δ 4.5, of the asymmetric carbon), and elemental analysis of the 2,4-dinitrophenylhydrazone derivatives. The analysis of gas remaining in the reactor after completion of the reaction showed the presence of carbon dioxide and a little ethylene. From these results, the reaction may be described as follows.

$$RCH{=}CH_2 + CO + NH_3 \xrightarrow[CH_3OH-H_2O]{Rh_2O_3}$$



In these reactions, the ring carbons of the imidazole ring and the asymmetric carbon of the ketoamide group apparently arise from carbon monoxide. These carbons are probably introduced as carbonyl groups first and then reduced with the aid of the rhodium catalyst.

It is well known that cobalt and rhodium carbonyls are the active catalysts in the carbonylation reaction,[2] and Heck has suggested that $HM(CO)_3$ (M = Co, Rh) is the active species in the catalytic carbonylation.[3]

However, cobalt carbonyl has not shown any catalytic activity for the formation of imidazole rings.

Furthermore, one of the present authors has shown recently that carbon monoxide is easily oxidized to carbon dioxide by a rhodium complex.[4] On the basis of these results, the formation of $HRh(CO)_3$ is assumed to occur as shown below. A similar mechanism of

$$\tfrac{1}{2}Rh_4(CO)_{12} + H_2O + CO \longrightarrow 2HRh(CO)_3 + CO_2$$

hydrorhodium carbonyl formation is found in the reaction of ethylene with carbon monoxide.[5]

Thus, $HRh(CO)_3$ adds to olefin to give an σ-alkyl rhodium carbonyl, which rearranges to an acyl rhodium complex and dimerized to yield an α diketone as reported by Tsutsumi.[6]

(1) K. Hofmann, "The Chemistry of Heterocyclic Compounds," Interscience, New York, N. Y., 1953.

(2) C. W. Bird, "Transition Metal Intermediates in Organic Synthesis," Logos Press, London, 1967.

(3) R. F. Heck, "Mechanism of Inorganic Reactions," American Chemical Society, Washington, D. C., 1965.

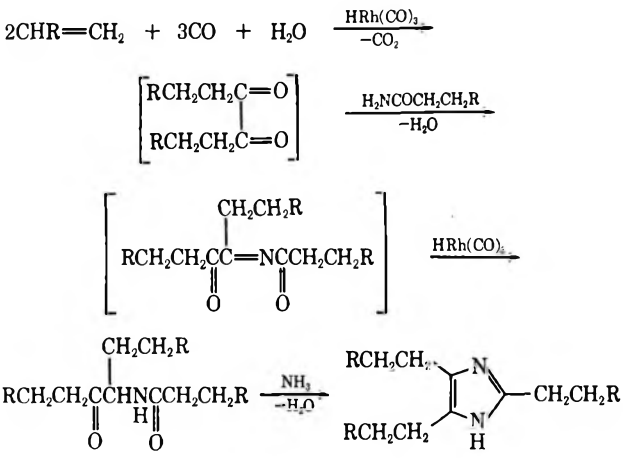
(4) Y. Iwashita and A. Hayata, *J. Amer. Chem. Soc.*, **91**, 2525 (1969).

(5) Y. Iwashita and M. Sakuraba, *Tetrahedron Lett.*, 2409 (1971).

(6) M. Ryang, S. Kwang-Myeong, Y. Sawa, and S. Tsutsumi, *J. Organometal. Chem.*, **5**, 305 (1966).

From these discussions Scheme I is suggested. This reaction course was supported by the formation of 2,4-diethyl-5-methylimidazole from pentane-2,3-dione and propionamide under a similar reaction condition.

SCHEME I



The multifunctional activity of rhodium, as a carbonylation catalyst in the first stage of the reaction and subsequently as a reduction catalyst, make the one-step imidazole ring formation possible from olefins, carbon monoxide, and ammonia.

Application of this reaction to propylene and 1-butene gives 2,4,5-tripropylimidazole in 59% and 2,4,5-tributylimidazole in 40% yields, respectively.

However, cyclohexene gives cyclohexanecarbonamide, *N*,*N*-di(cyclohexylmethyl)formamide, *N*,*N*-di(cyclohexylmethyl)methylamine, and tri(cyclohexylmethyl)-amine, as shown in Scheme II. The reaction products are similar to those obtained by reaction of cyclohexene with carbon monoxide and ammonia in the presence of cobalt carbonyl.[7] This fact is considered to be due to the difference of reactivity between terminal and internal olefins.

Experimental Section

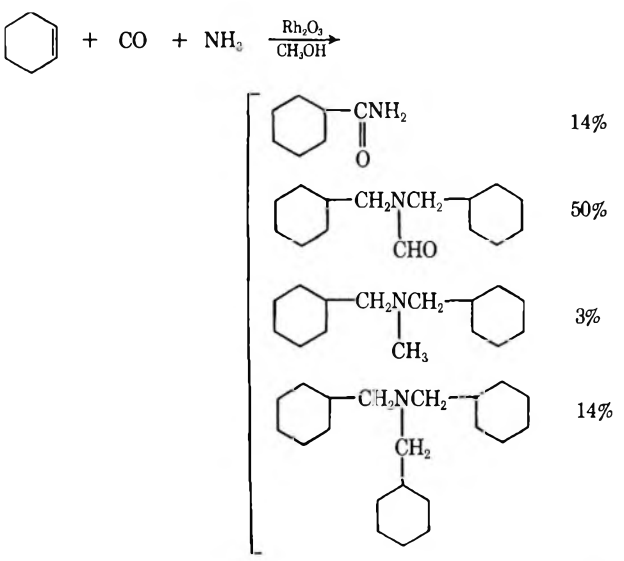
2,4,5-Trialkylimidazole Derivatives.—Rhodium oxide (50 mg) was suspended in aqueous methanol and placed in a 300-ml stainless steel autoclave. Propylene (32 g), ammonia (17 g), and carbon monoxide (250 kg/cm²) were introduced and the reaction was carried out at 150° for 5 hr. From the reaction mixture, 2,4,5-tripropylimidazole (29.3 g) was obtained by distillation, bp 125° (1 mm), in 59% yield.

Identification was made from its mass (*m/e* 194, 179, 165), uv [(C_2H_5OH) λ_{max} 220 and 278 nm], ir, and nmr spectra.

Anal. Calcd for $C_{12}H_{22}N_2$: C, 74.17; H, 11.41; N, 14.42. Found: C, 74.20; H, 11.64; N, 14.32.

(7) V. A. Striegler and J. Weber, *J. Prakt. Chem.*, **4**, 281 (1965).

SCHEME II



The same procedure was applied for ethylene and 1-butene, and 2,4,5-triethylimidazole, bp 119–123° (1 mm), and 2,4,5-tributylimidazole, bp 142–148° (0.6 mm), were obtained, in 59 and 52% yield, respectively.

Identification of 2,4,5-triethylimidazole was made from the mass (*m/e* 152, 137, and 123), uv, nmr (three different ethyl groups), and ir spectra.

Anal. Calcd for $C_9H_{16}N_2$: C, 70.99; H, 10.61; N, 18.40. Found: C, 70.91; H, 10.92; N, 18.30.

***N*-Propionyl-3-amino-4-hexanone.**—Methanol (40 ml) and 28% ammonia aqueous solution (15 ml), in which rhodium oxide (50 mg) was suspended, were placed in a 100-ml stainless steel autoclave. In the reactor ethylene (0.33 mol) and carbon monoxide (260 kg/cm²) were introduced and this vessel was heated for 4 hr at 130° (pressure drop about 200 kg). By distillation [117–125° (1 mm)], *N*-propionyl-3-amino-4-hexanone (7.6 g) was obtained in 40% yield. Identification was done by ir (ester C=O 1720, amide C=O 1650 cm^{-1}) and nmr (described before) spectra, and elemental analysis as the 2,4-dinitrophenylhydrazone.

Anal. Calcd for $C_{15}H_{20}N_4O_8$: C 51.27; H, 6.02; N, 19.93. Found: C, 51.34; H, 6.17; N, 19.72.

Reaction of Pentane-2,3-dione with Propionamide.—Pentane-2,3-dione (30 g) and propionamide (20 g) were added to a methanolic ammonia solution, in which rhodium oxide (50 mg) was suspended, and were allowed to react at 150° for 10 hr under a pressure of 150 kg/cm² of carbon monoxide. 2,4-Diethyl-5-methylimidazole was obtained and identified by nmr and mass spectra (*m/e* 152, 137, 123) and elemental analysis.

Registry No.—Carbon monoxide, 630-08-0; ammonia, 7664-41-7; 2,4,5-tripropylimidazole, 32044-26-1; 2,4,5-triethylimidazole, 32044-27-2; 2,4,5-tributylimidazole, 32044-28-3; *N*-propionyl-3-amino-4-hexanone, 32044-29-4.

Acknowledgment.—We thank Dr. A. Nakamura, Dr. M. Kainosho, and Dr. H. Wakamatsu for invaluable discussions.

Synthesis of Pyrrolo[2,3-*b*]pyrrole Derivatives[1]

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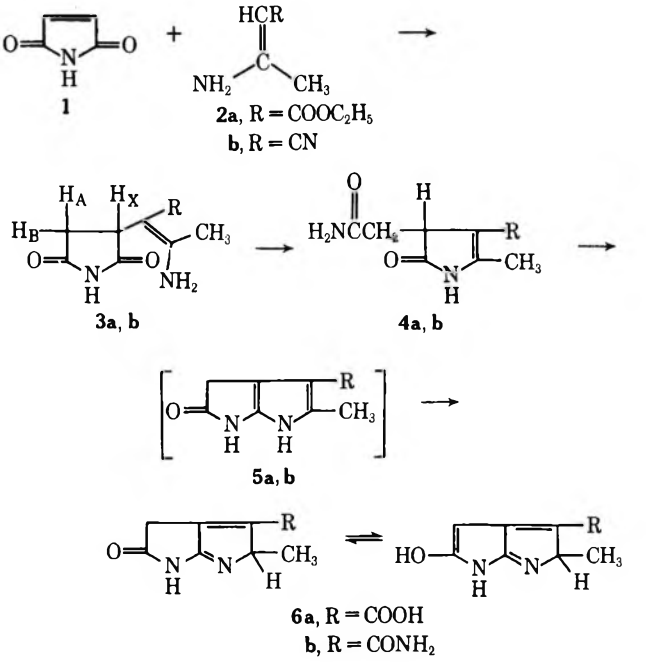
Received March 4, 1971

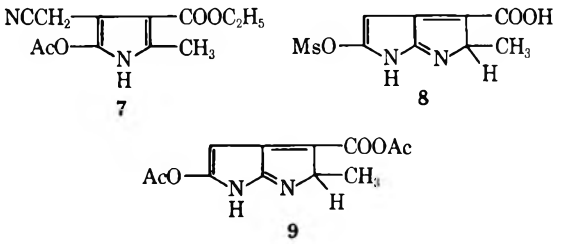
Reaction of maleimide and ethyl 3-aminocrotonate gives the aminovinylsuccinimide **3a**. On heating, **3a** is converted to the pyrrolinonacetamide **4a**. Treatment of **4a** with Ac_2O gives the 2-acetoxypyrrole-3-acetonitrile **7**. In base, **4a** undergoes cyclization to the pyrrolopyrrole **6**. Analogous compounds were obtained from maleimide and 3-aminocrotononitrile.

In recent years considerable attention[2] has been given to the applicability of the Nenitzescu synthesis[3] for the preparation of 5-hydroxy-3-carbalkoxyindole derivatives. The general route involves the condensation of a 1,4-benzoquinone with an appropriate 3-aminocrotonate. Our interest in the construction of various nitrogen, oxygen, and sulfur isosteres of biologically active indole-containing compounds led us to investigate the feasibility of extending this reaction to the synthesis of pyrrolo[2,3-*b*]pyrrole derivatives.

When one considers that the sulfur atom is isosteric with a vinyl group (ring equivalents)[4] and that the oxygen and nitrogen (–NH–) atoms are isosteric with sulfur or the vinyl group, then maleimide, maleic anhydride, or thiomaleic anhydride[5] may be expected to behave chemically as isosteres of 1,4-benzoquinone. In fact, maleimide and maleic anhydride have been described as pyrrolequinone and furanquinone in some early work.[6] Maleimide (**1**) was chosen for our initial studies, and its reaction with ethyl 3-aminocrotonate (**2a**) gave a product (**3a**), mp 156–158°. Structural assignment was made from infrared, nmr, and elemental analysis data. From previous experience with the Nenitzescu reaction, one would have anticipated direct isolation of the pyrrolo[2,3-*b*]pyrrole (**5**), but in this case a possible intermediate (**3a**) proposed to occur in the reaction sequence was isolated and characterized. Heating of **3a** in xylene (or organic solvents boiling above 100°) gave a product (**4a**), mp 231–234°, as anticipated when an amine is heated with an imide.[7] Intermediates analogous to **3a** and **4a** have been described by Robson and Marcus[8] when maleic anhydride was treated with 3-methylaminocrotonate. Structural assignment for **4a** was confirmed by infrared, elemental analysis, and nmr data. The coupling for **4a** (see Experimental Section) was similar to that observed for 3-carbomethoxy-1,2-dimethyl-5-oxo-2-pyrroline-4-acetic acid[8] and 3-carbethoxy-2,4-dimethyl-5-oxo-2-pyrroline.[9]



Conditions designed to convert **4** into **5** (*e.g.*, refluxing in ethylene glycol with a trace of sulfuric acid or acid alone) gave almost quantitatively recovery of starting material. When **4a** was refluxed in acetic anhydride, an enol acetate **7**[10] resulted with dehydration of the amido function. However, in basic solutions (30% potassium hydroxide, concentrated ammonium hydroxide, or alcoholic potassium *tert*-butoxide), a reaction was achieved, and the product from **4a** was identified as **6a**. This substance (**6a**) was probably formed *via* the intermediate **5a**, which hydrolyzed to the carboxylic acid upon work-up. Protonation of **5a** to give a hydrogen at the 2 position can occur through enamine behavior of the pyrrole ring upon work-up under acidic



(1) This work was supported by Research Grant MH-16422 from the National Institutes of Health. Presented at the 160th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1970, Abstract ORGN 78.

(2) (a) M. J. Weiss, G. R. Allen, Jr., G. J. Gibs, C. Pidacks, J. F. Poletto, and W. A. Remers in "Topics in Heterocyclic Chemistry," R. N. Castle, Ed., Wiley–Interscience, New York, N. Y., 1969, p 178; (b) S. A. Monti, *J. Org. Chem.*, **31**, 2669 (1966); (c) R. Littell, G. O. Morton, and G. R. Allen, Jr., *J. Amer. Chem. Soc.*, **92**, 3740 (1970); (d) J. F. Poletto and M. J. Weiss, *J. Org. Chem.*, **35**, 1190 (1970).

(3) C. D. Nenitzescu, *Bull. Sci. Chim. Romania*, **11**, 37 (1929); *Chem. Abstr.*, **24**, 110 (1930).

(4) V. B. Schatz in "Medicinal Chemistry," 2nd ed, A. Burger, Ed., Interscience, New York, N. Y., 1960, p 72.

(5) (a) J. Z. Mortensen and S. O. Lawesson, *Acta Chem. Scand.*, **22**, 1056 (1968); (b) H. D. Scharf and M. Verbeek, *Angew. Chem., Int. Ed. Engl.*, **6**, 874 (1967).

(6) (a) P. Pfieffer and T. Bottler, *Ber.*, **51**, 1819 (1918); (b) G. Plancher and F. Cattadori, *Atti Accad. Naz. Lincei*, **13**, 489 (1904); *J. Chem. Soc.*, **86**, 770 (1904).

(7) (a) A. L. J. Beckwith in "The Chemistry of Amides," J. Zabicky, Ed., Interscience, New York, N. Y., 1970, pp 116–117; (b) H. Zimmer, *Tetrahedron Lett.*, 2839 (1970).

(8) J. H. Robson and E. Marcus, *Chem. Ind. (London)*, 1022 (1970).

(9) J. H. Atkinson, R. S. Atkinson, and A. W. Johnson, *J. Chem. Soc.*, 5999 (1964).

(10) T. Kato, M. Sato, and T. Yoshida, *Chem. Pharm. Bull.*, **19**, 292 (1971).

conditions. Although the alkaline conditions employed for conversion of **4** to **5** are not common in ring closure procedures utilized for synthesis of pyrroles or indoles, they are often useful for preparation of compounds with the -NCN- moiety. For example, numerous 4-oxoquinazolines,[11] benzimidazoles,[12] and purines[13] can be prepared by heating amides in aqueous or alcoholic alkali for base-catalyzed dehydrocyclization.[14] Furthermore, it is possible that **4** may be reconverted to **3** under the alkaline conditions since the process is reversible,[7a] and that **3** is the actual substance which undergoes base-catalyzed cyclodehydration Many examples may be cited[12,14,15] for reaction of an amide carbonyl with an amine. Compound **6a** was, in fact, prepared directly from **3a** (method B).

Structural assignment for **6** was confirmed by nmr spectroscopy where an enol form appears to predominate in highly polar solution while the keto form appears to be favored in solid phase infrared studies. The facility of the enolization is substantiated by deuterium exchange studies. The C-4 proton(s) at δ 5.79 in the enol form is exchanged, as well as the NH and OH protons for **6a** (and **6b**), but, when O-substituted derivatives (*e.g.*, mesylate **8** and acetate **9**) are prepared and tautomerism is prohibited, the C-4 proton at δ 6.86 (**8**) or 7.48 (**9**) is not exchanged. (In addition to elemental and spectral data, structural assignment for **7** and **9** was supported by observation that **7** did not react with 2,4-dichloroaniline, but the anhydride **9** gave 2,4-dichloroacetanilide.) The carboxyl (**6a**) proton is not easily assigned because of exchange with solvent. Irradiation of the doublet at δ 1.40 (**6a**) led to collapse of the quartet at 4.45, with similar results being obtained for **6b**.

From the elemental analysis of **6a**, it was difficult to obtain a sample completely devoid of all traces of water, the presence of moisture being confirmed by the Karl Fischer method. (For an analytical sample devoid of water and acceptable for elemental analysis, it was necessary to dry the material *in vacuo* at 100° over phosphorus pentoxide for 2 weeks.) To eliminate this problem and obtain acceptable elemental analysis, without the need to include water in the calculated values, a derivative was prepared to avoid the presence of a carboxylic acid moiety (the hygroscopic moiety). Maleimide was allowed to react with 3-aminocrotonitrile (**2b**) in the hope that the cyano moiety would reduce or eliminate the affinity of the analytical sample to retain moisture. Intermediates similar to **3a** and **4a** were isolated and characterized. The conversion of **4b** to **6b** was achieved in basic solution with alcoholic potassium *tert*-butoxide giving best results. Again, work-up conditions gave a hydrolysis product; nitrile converted to the amide. An nmr spectrum supported the structural assignment and the analytical sample was devoid of moisture contamination.

Preliminary evidence indicated that the ring system was quite stable under acidic or basic condition. For example, **6a** dissolved in warm concentrated sulfuric acid and precipitated as a sulfate salt on addition of cold ethyl acetate. Upon addition of this salt to water or alcohol, solution was immediately achieved, followed in a short period by precipitation of the starting product (**6a**). A weak salt complex was apparently formed and readily hydrolyzed to the parent material without destruction or alteration of the basic ring system. However, **6a** was observed to be quite susceptible to oxidative or thermal decomposition. Routine decarboxylation attempts or warming in dimethyl sulfoxide gave black or blue-purple amorphous material with the odor of dimethyl sulfide being detected in the latter instance. Structural assignment has not been made for the product of these reactions.

With the successful application of the modified Nenitzescu reaction for the synthesis of the pyrrolo[2,3-*b*]-pyrrole ring, the parent nucleus with suitable functional groups is now available for the preparation of various indole isosteres of biologically active agents. The results of these studies, as well as additional data on the chemical behavior of the new heterocycle and applicability of maleic anhydride and thiomaleic anhydride[16] in the reaction, will constitute future communication.

Experimental Section

Melting points were determined on a Thomas-Hoover apparatus (capillary method) and are uncorrected. The nmr spectra were determined on a Hitachi Perkin-Elmer R 20A high-resolution nmr spectrometer using DMSO-d_6 as solvent and tetramethylsilane as internal reference. Elemental analyses were by Galbraith Laboratories, Inc., Knoxville, Tenn., or Atlantic Microlab, Inc., Atlanta, Ga. Infrared spectra were measured on a Perkin-Elmer 237 B grating spectrophotometer using the potassium bromide technique, and ultraviolet spectra were determined in methanol solution with a Perkin-Elmer 202 ultraviolet–visible spectrophotometer. Tlc was performed on Eastman chromatogram sheets, type 6060.

Ethyl 3-[α-(1-Aminoethylidene)]-2,5-dioxopyrrolidineacetate (3a).—A solution of 77.6 g (0.08 mol) of maleimide and 100 g of ethyl 3-aminocrotonate in 450 ml of acetone was heated at reflux for 18–24 hr with continuous stirring. The acetone was removed *in vacuo*, and the white solid was collected, washed with petroleum ether (80–93% yield), and crystallized from ethanol (homogeneous on tlc, $CHCl_3$): mp 156–158°; ir (KBr) 3450, 3400, 3300, 3250, 1780, 1720, 1650, 1620, 1540 cm^{-1}; nmr δ 1.10 (t, 3 H, J = 7.5 Hz, CH_3 of ethyl), 2.00 (s, 3 H, vinyl methyl), 2.35 (CH_A, 1 H, J_{AX} = 6.0 Hz), 2.92 (CH_B, 1 H, J_{AB} = −17.0 Hz), 3.73 (CH_X, 1 H, J_{BX} = 9.0), 3.95 (q, 2 H, J = 7.5; CH_2 of ethyl), 6.5–8.5 (broad d, 2 H, NH_2), and 10.8 (broad s, 1 H, NH) (NH_2 and NH exchanged by D_2O); uv max (MeOH) 205 mμ (ϵ 4970) and 284 (14,800).

Anal. Calcd for $C_{10}H_{14}N_2O_4$: C, 53.05; H, 6.19; N, 12.38. Found: C, 53.07; H, 6.19; N, 12.43.

3-Carbethoxy-2-methyl-5-oxo-2-pyrroline-4-acetamide (4a).—A suspension of **3a** (25 g, 0.111 mol) in 150 ml of xylene with a trace of piperidine was refluxed and stirred for 2 hr. (Dissolution of the starting material was not achieved.) Upon cooling, a lavender-colored product (mp 218–226°) was filtered from a reddish blue mixture (85–90% yield). The product was crystallized from ethanol–DMF (9:1) or from hot water as a tan material and found to be homogenous on tlc ($CHCl_3$; substance had

(11) W. L. F. Armarego in "Quinazolines: Fused Pyrimidines, Part I," D. J. Brown, Ed., Interscience, New York, N. Y., 1967, pp 78–80.

(12) (a) G. McCoy and A. R. Day, *J. Amer. Chem. Soc.*, **65**, 2159 (1943); (b) J. D. Loundon in "Chemistry of Carbon Compounds," Vol IVa, E. H. Rodd, Ed., Elsevier, New York, N. Y., 1957, p 322.

(13) (a) E. Shaw, *J. Biol. Chem.*, **185**, 439 (1950); (b) T. Ichikawa, T. Kato, and T. Takenishi, *J. Heterocycl. Chem.*, **2**, 253 (1965); (c) G. A. Howard in "Chemistry of Carbon Compounds," Vol. IVc, E. H. Rodd, Ed., Elsevier, New York, N. Y., 1960, p 1647.

(14) (a) B. R. Baker and D. V. Santi, *J. Heterocycl. Chem.*, **4**, 216 (1967); (b) W. J. Haggerty, Jr., R. H. Springer, and C. C. Cheng, *J. Med. Chem.*, **8**, 797 (1965).

(15) (a) R. G. Glushkov and O. Yu Magidson, *Zh. Obshch. Khim.*, **30**, 1855 (1960); *J. Gen. Chem. USSR*. **30**, 1838 (1960); (b) A. J. Hill and S. R. Aspinall, *J. Amer. Chem. Soc.*, **61**, 822, 3195 (1939); (c) H. Brecereck and G. Theilis, *Ber.*, **86**, 88 (1953); *Angew. Chem.*, **71**, 753 (1959).

(16) Reference 8 and an abstract[17] have appeared describing the preparation of 5-oxo-2-pyrrolines by reaction of 3-alkylaminocrotonates with maleic anhydride. These reports may indicate a limited scope in the modified Nenitzescu reaction for synthesis of furo[2,3-*b*]pyrroles.

(17) S. G. Agbalyan and L. A. Nersesyan, *Arm. Khim. Zh.*, **22**, 40 (1969); *Chem. Abstr.*, **71**, 91195 (1969).

a greenish fluoresence in solution and bluish on paper under uv light): mp 231–234° dec; ir (KBr) 3350, 3230, 3175, 2975, 1740, 1660, 1625 cm^{-1}; nmr δ 1.20 (t, 3 H, J = 7.5 Hz, CH_3 of ethyl), 2.25 (d, 3 H, J = 2.0 Hz 2-CH_3), 2.52 (d, 2 H, J = 5.0 Hz, 4-CH_2), 3.31 (t, 1 H, J = 5.0 Hz, C_4H) (triplet split into multiplet, J = 2.0 Hz), 4.06 (q, 2 H, J = 7.5 Hz, CH_2 of ethyl), 7.2–6.61 (broad d, 2 H, amido NH_2), and 10.2 (broad s, 1 H, NH) (NH and NH_2 protons exchanged by D_2O); uv max (MeOH) 205 mμ (ϵ 4070), 220 (3840), and 282 (10,500).

Anal. Calcd for $C_{10}H_{14}N_2O_4$: C, 53.05; H, 6.19; N, 12.38. Found: C, 52.77; H, 6.20; N, 12.41.

5-Acetoxy-3-carbethoxy-2-methylpyrrole-4-acetonitrile (7).—The amide **4a** (2 g) was suspended in 50 ml of acetic anhydride and refluxed for 2 hr. Solution occurred after 45 min when the oil bath temperature had reached 150°. After standing overnight, the solvent was concentrated *in vacuo*. The residual oil was washed with petroleum ether, treated with a few milliliters of ethanol, and diluted with water. On standing, a pale yellow solid separated. The analytical material (25–45%) was crystallized from 95% ethanol: mp 139–141°; ir (KBr) 3200, 2260, 1775, 1700, 1630 cm^{-1}; nmr δ 1.30 (t, 3 H, J = 7.5 Hz, CH_3 of ethyl), 2.3 (s, 3 H, 2-CH_3), 2.38 (s, 3 H, CH_3 of acetoxy), 3.65 (s, 2 H, 4-CH_2), 4.20 (q, 2 H, J = 7.5 Hz, CH_2 of ethyl), 11.70 (broad s, 1 H, NH, exchanged by D_2O).

Anal. Calcd for $C_{12}H_{14}N_2O_4$: C, 57.60; H, 5.60; N, 11.20. Found: C, 57.52; H, 5.79; N, 11.08, 11.16.

2,4,5,6-Tetrahydro-2-methyl-5-oxopyrrolo[2,3-*b*]pyrrole-3-carboxylic Acid (6a). Method A.—**4a** (15 g, 0.067 mol) suspended in 200 ml of *tert*-butyl alcohol was treated with 8 g of potassium *tert*-butoxide and refluxed for 4.5 hr. (The solid dissolved almost immediately on heating, then the reaction mixture became cloudy, and eventually a thick voluminous brown product precipitated.) A major portion of the *tert*-butyl alcohol was removed *in vacuo* leaving a pale yellow solid residue. The semidry residue was added to 200 ml of cold 2 *N* H_2SO_4 and then diluted to 400 ml with water. The resulting yellow solution was stirred and chilled to achieve precipitation of a pale yellow product from the dark greenish solution. Addition of potassium chloride facilitated precipitation of the desired product. After standing overnight, the yellow-tan product was collected (70–85% yield). After crystallization from hot water, the compound which was bicarbonate soluble, melted at 253–255° dec (sealed tube) and was homogenous on tlc (MeOH–Et_2NH, 19:1). For analysis, a sample was repeatedly purified by dissolution in sodium hydroxide, subsequent acidification with dilute sulfuric acid, and drying over P_2O_5: mp 255–257° dec (sealed tube); ir (KBr) 3300, 3150–2700 (broad, m), 1700, 1650, 1600 cm^{-1}; nmr δ 1.40 (d, 3 H, J = 6.5 Hz, 2-CH_3), 4.45 (q, 1 H, J = 6.5 Hz, C_2H), 5.79 (s, 1 H, C_4H), 8.90 (s, 1 H, NH) (peaks at 5.79 and 8.90 exchanged by D_2O); mol wt (mass spectrometry) 180 (calcd 180); uv max (MeOH) 209 mμ (ϵ 12,300), 233 (9810), and 339 (6660).

Anal. Calcd for $C_8H_8N_2O_3$: C, 53.33; H, 4.44; N, 15.55. Found (0.5 H_2O): C, 50.38; H, 5.04; N, 14.66. Found (after drying 10 days *in vacuo* and over P_2O_5): C, 53.16; H, 4.51; N, 15.54.

Method B.—In this procedure, **3a** was substituted for **4a** in method A with the result that **6a** was obtained in 71–87% yield. The product from either method had identical ir, nmr, and melting point.

Preparation of a solid ester derivative from phenacyl bromide[18] gave a disubstituted product, *i.e.*, reaction with the 3-carboxylic acid and the 5-enolic moiety. Upon crystallization from ethanol–DMF, a white product was obtained, melting at 260–262° (seal tube): ir (KBr) 3350, 1700 (broad), 1680, 1600 cm^{-1}.

Anal. Calcd for $C_{24}H_{20}N_2O_5$: C, 69.23; H, 4.81; N, 6.74. Found: C, 69.34; H, 4.89; N, 6.68.

2,6-Dihydro-3-carboxyl-2-methylpyrrolo[2,3-*b*]pyrrole-5-mesylate (8).—**6a** (5 g, 0.028 mol) was suspended in 50 ml of water and treated with 1.22 g (0.031 mol) of sodium hydroxide. This solution was treated with 2.4 ml (0.031 mol) of methanesulfonyl chloride. A brown solid began to precipitate almost immediately. After the solution was stirred for 30 min, product was collected (65–95%) and recrystallized from 95% ethanol: mp 205° dec; ir (KBr) 3360, 3000–2600 (broad), 1690, 1650, 1625, 1350, 1180 cm^{-1}; uv max (MeOH) 207 mμ (ϵ 14,300), 218 (10,900), 242 (4930), and 295 (6220); nmr δ 1.40 (d, 3 H, J = 6.5 Hz, 2-CH_3), 3.52 (s, 3 H, CH_3 of mesyl), 4.65 (q, 1 H, J = 6.5 Hz, C_2H), 6.86 (s, 1 H, C_4H), 9.08 (s, 1 H, NH), and 12.25 (broad s, 1 H, COOH, undergoes slow exchange with solvent on standing) (Peaks at 9.08 and 12.25 exchanged with D_2O).

Anal. Calcd for $C_9H_{10}N_2O_5S$: C, 41.86; H, 3.87; N, 10.85; S, 12.40. Found: C, 42.02; H, 3.99; N, 10.78; S, 12.33.

5-Acetoxy-2,6-dihydro-2-methylpyrrolo[2,3-*b*]pyrrole-3-carboxylic Ethanoic Anhydride (9).—The pyrrolopyrrole **6a** (1 g) was suspended in 35 ml of acetic anhydride and heated at 75–80° for 1.5 hr. The grey suspension became yellowish and as the temperature was increased to 110° over 0.5 hr a red solution occurred. After an additional 20 min at 110°, the hot solution was filtered and allowed to stand overnight. Excess acetic anhydride was removed *in vacuo* and the residual syrup treated with 5 ml of ethanol and 50 ml of water. After salting with NaCl, a pale purplish material separated, mp 122–130°, 0.98 g. An analytical sample crystallized from $CHCl_3$–ligroine: mp 149–151° (sealed tube); ir (KBr) 3180, 3140, 3100, 3075, 1775, 1760, 1724, 1710, 1625, 1580 cm^{-1}; nmr δ ($CDCl_3$) 1.49 (d, 3 H, J = 6.5 Hz, 2-CH_3), 2.33 (s, 3 H, C_5 acetoxy), 2.35 (s, 3 H, CH_3 of anhydride), 4.70 (q, 1 H, J = 6.5 Hz, C_2H), 7.48 (s, 1 H, C_4H), and 8.72 (s, 1 H, NH, exchanged by D_2O).

Anal. Calcd for $C_{12}H_{12}N_2O_5$: C, 54.55; H, 4.55; N, 10.61. Found: C, 54.65; H, 4.57; N, 10.73.

3-[α-(1-Aminoethylidene)]-2,5-dioxopyrrolideneacetonitrile (3b).—The procedure described for preparation of **3a** was utilized in the condensation of maleimide and 3-aminocrotonitrile. The product (40–50% yield) was crystallized from ethanol: mp 173–175°; ir (KBr) 3450, 3350, 3250–3100 (broad), 2200, 1800, 1700, 1660, 1625 cm^{-1}; nmr δ 2.02 (s, 3 H, vinyl methyl), 2.35 (CH_A, 1 H, J_{AX} = 5.5 Hz), 3.05 (CH_B, 1 H, J_{AB} = −18.0 Hz), 3.89 (CH_X, 1 H, J_{BX} = 9.0 Hz), 6.55 (s, 2 H, NH_2), and 11.25 (s, 1 H, NH); uv max (MeOH) 204 mμ (ϵ 3400) and 259 (10,400).

Anal. Calcd for $C_8H_9N_3O_2$: C, 53.63; H, 5.03; N, 23.46. Found: C, 53.43; H, 5.11; N, 23.33.

3-Cyano-2-methyl-5-oxo-2-pyrroline-4-acetamide (4b).—This product (**4b**) could be prepared by the procedure described for **4a** in refluxing xylene. However, it was more convenient to prepare **4b** directly without isolating **3b**. A solution containing 1 mol of maleimide was treated with 1.2 mol of 3-aminocrotonitrile in 400 ml of dioxane and refluxed for 48 hr. The dioxane was then removed *in vacuo* and the remaining brown gummy residue was boiled with ethanol. The insoluble substance was collected by filtration, washed with ethanol, and dried (mp 252–253°). Crystallization from ethanol–DMF (yield 37–51%) gave a product which melted at 253–255°: ir (KBr) 3400, 3300, 2200, 1720, 1670, 1620 cm^{-1}; nmr δ 2.10 (d, 3 H, J = 2 Hz, 2-CH_3), 2.55 (d, 2 H, J = 5 Hz, 4-CH_2), 3.45 (t, 1 H, J = 5 Hz, C_4H) (triplet split into multiplet, J = 2.0 Hz), 7.15 (broad d, 2 H, amido NH_2), and 10.50 (broad s, 1 H, NH); uv max (MeOH) 206 mμ (ϵ 2540), 270 (5150), 275 (5520), and 279 (5300).

Anal. Calcd for $C_8H_9N_3O_2$: C, 53.63; H, 5.03; N, 23.46. Found: C, 53.50; H, 4.95; N. 23.59.

The alcoholic filtrate was concentrated to 1/3 the original volume and then diluted with water to give an off-white product melting at 300–304°. Upon crystallization from dioxane this substance melted at 302–304° and was homogenous on tlc ($CHCl_3$–CH_3OH, 2:1). This product was assigned the structure 2,6-dimethyl-4-oxonicotinonitrile:[19] ir (KBr) 3000–2700 (broad), 2215, 1680, 1620, 1570 cm^{-1}; nmr δ 2.2 (d, 3 H), 2.4 (s, 3 H), 6.18 (m, 1 H), 12.2 (broad, 1 H, NH) (both CH_3 peaks are weakly coupled to the CH at 6.18).

Anal. Calcd for $C_8H_8N_2O$: C, 64.86; H, 5.41; N, 18.92. Found: C, 65.20; H, 5.63; N, 18.79.

2,4,5,6-Tetrahydro-2-methyl-5-oxopyrrolo[2,3-*b*]pyrrole-3-carboxamide (6b).—**4b** (15 g, 0.083 mol) suspended in 150 ml of *tert*-butyl alcohol was treated with 10.1 g (0.09 mol) of potassium *tert*-butyl alcohol and refluxed for 14 hr under constant stirring. The mixture was concentrated *in vacuo* and the solid residue added

(18) (a) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 4th ed, Wiley, New York, N. Y., 1960, p 200; (b) J. B. Hendrickson and C. Kandall, *Tetrahedron Lett.*, 343 (1970).

(19) E. V. Meyer and C. Irmscher, *J. Prakt. Chem.*, **78**, 523 (1908). In this reference, the 2,6-dimethyl-4-oxonicotinonitrile was reportedly synthesized from 3-aminocrotonitrile (diacetonitrile) and ethyl acetoacetate in presence of pyridine. No mention was made of synthesis from self-condensation of 3-aminocrotononitrile, which can be easily accomplished (60–70% yield) by refluxing in 90% ethanol with piperidine catalysis. Structural assignment also supported by comparison with known[20] 4,6-dimethyl-2-oxonicotinonitrile.

(20) H. O. Fitton and R. K. Smalley in "Practical Heterocyclic Chemistry," Academic Press, New York, N. Y., 1968, p 71.

to 200 ml of water containing 5.8 ml of acetic acid. After standing for 1 hr, the precipitate was collected and washed with cold water. The crude product (mp 319°, 62–74% yield) was crystallized from hot water (25–50% yield): mp 347°; ir (KBr) 3350 (broad), 3180 (broad), 2880 (broad), 1720, 1680, 1650 (broad), 1600 cm^{-1}; nmr δ 1.29 (d, 3 H, J = 6 Hz, 2-CH_3), 4.42 (q, 2 H, J = 6 Hz, C_2H), 5.71 (s, 1 H, C_4H), 6.23 (s, 2 H, amido NH_2), 8.72 (s, 1 H, NH), and 10.63 (broad s, 1 H, 5-OH); uv max (MeOH) 211 mμ (ϵ 12,000), 240 (9750), and 370 (7360).

Anal. Calcd for $C_8H_9N_3O_2$: C, 53.63; H, 5.03; N, 23.46. Found: C, 53.75; H, 5.14; N, 23.58.

It was observed that fairly pure **6b** could be prepared simply by warming **4b** in 30% KOH for 20 min at 80°, followed by acidification with 6 *N* HCl (mp 342°, 36% yield).

Registry No.—**3a**, 31926-73-5; **3b**, 31926-74-6; **4a**, 31926-75-7; **4b**, 31926-76-8; **6a** (keto), 31926-77-9; **6a** (enol), 31926-78-0; **6b** (keto), 31926-79-1; **6b** (enol), 31926-80-4; **7**, 31926-81-5; **8**, 31926-82-6; **9**, 31926-83-7; 2,6-dimethyl-4-oxonicotenonitrile, 31926-84-8.

Acknowledgment.—We wish to thank Mrs. Patricia Holbrook and Mr. Oswald Mayer for their technical assistance. We are indebted to Drs. L. C. Martinelli, B. B. Thompson, and I. L. Honigberg for helpful discussion.

A Simple Synthetic Route to Benzo[*c*]thiophene and the Naphtho[*c*]thiophenes

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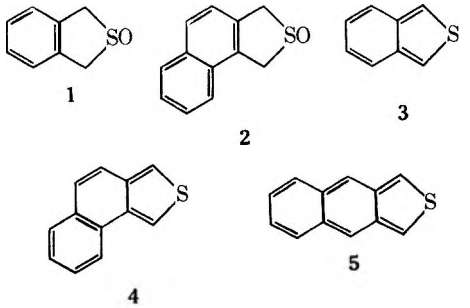
Received April 20, 1971

Benzo[*c*]thiophene (isothianaphthene, **3**) was obtained when 1,3-dihydrobenzo[*c*]thiophene 2-oxide (**1**) was heated with neutral alumina to 120–130°. Thiophene **3** was generated *in situ* when sulfoxide **1** was heated with acetic anhydride, as shown by the isolation of the exo and endo Diels–Alder adducts **8** and **9**, when *N*-phenylmaleimide was present in the reaction mixture. Similarly, the stable new heterocycle naphtho[1,2-*c*]-thiophene (**4**) was formed by heating the corresponding sulfoxide **2** with neutral alumina; thiophene **4** formed the exo and endo adducts **16** and **17** by the addition of *N*-phenylmaleimide to the thiophene ring. In contrast, naphtho[2,3-c]thiophene (**5**) could not be prepared by the alumina pyrolysis of sulfoxide **19**, which yielded only trace amounts of the disproportionation products 1,3-dihydronaphtho[2,3-*c*]thiophene (**20**) and 1,3-dihydronaphtho[2,3-c]thiophen-1-one (**24**). Although it was too unstable to be isolated, thiophene **5** was generated by the dehydration of sulfoxide **19**, as evidenced by trapping experiments using *N*-phenylmaleimide; three adducts (**21**, **22**, and **23**) were isolated, the major two resulting from dienophile addition to the thiophene ring of **5** and the minor product resulting from dienophile addition to the central ring of **5**.

Some time ago we reported, in a preliminary communication, that the thermolysis of 1,3-dihydrobenzo-[*c*]thiophene 2-oxide (**1**) and 1,3-dihydronaphtho-[1,2-*c*]thiophene 2-oxide (**2**) led to dehydration with the formation of benzo[*c*]thiophene (isothianaphthene, **3**) and the previously unreported naphtho[1,2-*c*]thiophene (**4**).[2] In this paper further details of this work are described, as well as attempts to extend the sulfoxide dehydration method to the synthesis of the unknown *o*-quinonoid heterocycle naphtho[2,3-*c*]thiophene (**5**).



1 2 3 4 5

Benzo[*c*]thiophene.—The pyrolysis of 1,3-dihydrobenzo[*c*]thiophene 2,2-dioxide (**6**) leads to the extrusion of sulfur dioxide and the generation of the unstable *o*-quinodimethane (**7**), which can be trapped *in situ* by dienophiles or which under proper conditions cyclizes intramolecularly to give benzocyclobutene.[3–5] It seemed likely that the related sulfoxide 1,3-dihydrobenzo[*c*]thiophene 2-oxide (**1**)[6] might undergo a similar extrusion of sulfur monoxide to give the same transformation products of **7**.[7] Indeed, when a mixture of sulfoxide **1** and *N*-phenylmaleimide (NPM) was heated to 220° in the absence of a solvent, a vigorous reaction took place. The product was not the known NPM adduct[3] of hydrocarbon **7**, however, but a mixture of two sulfur-containing isomers $C_{18}H_{13}NO_2S$, which were subsequently shown to be the endo and exo adducts (**8** and **9**) of NPM with benzo[*c*]thiophene. The same adduct mixture was obtained more conveniently and in excellent yield (86%) by refluxing a mixture of NPM and sulfoxide **1** in acetic anhydride. The intermediacy of benzo[*c*]thiophene (**3**) in these reactions was confirmed by preparing adducts **8** and **9** by the direct addition of NPM to pure thiophene **3** in benzene solution.

The isomeric adducts **8** and **9** were assigned the exo and endo structures, respectively, on the basis of their nmr spectra. In the nmr spectrum of exo adduct **8**, the two protons α to the imide carbonyls appear at δ 3.30, a position similar to that (3.43) of the corresponding protons of the NPM–anthracene adduct **10**;[8] molecular models indicate similar environments for the protons in both compounds, with no shielding in either case. The two bridgehead protons of **8** appear at δ 4.93 and the

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(2) M. P. Cava and N. M. Pollack, *J. Amer. Chem. Soc.*, **88**, 4112 (1966).

(3) M. P. Cava and A. A. Deana, *ibid.*, **81**, 4266 (1959).

(4) J. A. Oliver and P. A. Ongley, *Chem. Ind. (London)*, 1024 (1965).

(5) For a general review of the chemistry of benzo[*c*]thiophenes, see B. Iddon, *Advan. Heterocycl. Chem.*, in press.

(6) An nmr study of sulfoxide **1** has appeared in the literature [R. F. Watson and J. F. Eastham, *J. Amer. Chem. Soc.*, **87**, 664 (1965)], but the preparation and properties of the compound were not reported.

(7) A related decomposition of some episulfoxides to sulfur monoxide and olefins has been reported: G. E. Hartzell and J. N. Paige, *ibid.*, **88**, 2616 (1966).

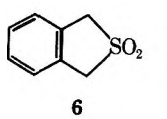
(8) M. P. Cava and R. H. Schlessinger, *Tetrahedron*, **21**, 3073 (1965).

nine aromatic protons are seen as a broad band in the δ 7.0–7.5 region.

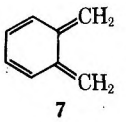
In endo adduct **9**, the protons α to the imide carbonyls appear at δ 4.10, as a result of a strong deshielding effect of the sulfur bridge. The bridgehead protons, in an environment similar to those in exo isomer **8**, appear at δ 4.90. Finally, only seven of the nine aromatic protons are seen in the expected δ 7.0–7.5 region; the remaining two appear far upfield as a broad band centered at δ 6.43. Molecular models explain this observation by showing that rotation of the phenyl substituent of **9** brings the two protons ortho to the nitrogen within the shielding zone of the opposite aromatic ring.[9] It is also of interest to note that the two sets of nonaromatic protons of exo isomer **8**, with a dihedral angle of about 90° (J = 0 Hz), appear as sharp singlets, while the corresponding protons of endo isomer **9**, with a smaller dihedral angle (and consequently appreciable value for J), are broadened.

Benzo[c]thiophene (**3**) has been synthesized previously only by the high-temperature catalytic dehydrogenation of its 1,3-dihydro derivative.[10] We have found that the dehydration of sulfoxide **1** is useful not only for the synthesis of adducts of **3** but is easily utilized as a practical new synthetic preparation of **3** itself. Thus, when a mixture of sulfoxide **1** and neutral alumina was heated under reduced pressure at 100–125° in a sublimer, almost pure benzo[c]thiophene (**3**) condensed on the cold finger in high yield (94%) as a white crystalline crust. Completely pure **3** could be obtained by resublimation, but the recovery was poor, apparently due to polymerization of this highly reactive heterocycle.[10]

It has been reported earlier that benzo[c]thiophene reacts with maleic anhydride to give an adduct, mp 153–154°, the stereochemistry of which was not determined.[10] In a brief reexamination of this reaction, we obtained a product, mp 148–152°, which was shown by nmr to be a mixture of the exo and endo isomers **11** and **12** in a ratio of 1:1.25. The protons α to the carbonyls in **11** and **12** appear at δ 3.55 and 4.29, respectively.



6



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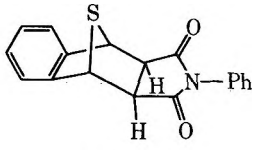
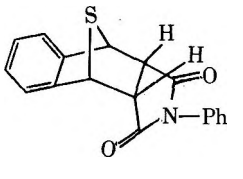
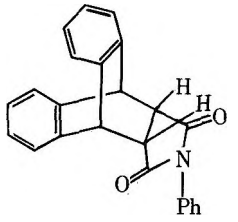


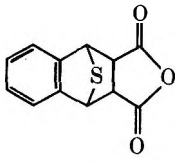
8 (exo)



9 (endo)



10



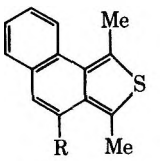
11 (exo)
12 (endo)

Naphtho[1,2-c]thiophene.—Prior to our study, the only known derivatives of naphtho[1,2-c]thiophene (**4**) were the 1,3-dimethyl derivative **13** and the corresponding 7-carboxylic acid (**14**); the preparation of these compounds required a multistep synthesis from 2,5-dimethylthiophene.[11] We found that dehydration of 1,3-dihydronaphtho[1,2-c]thiophene 2-oxide (**2**), prepared by the periodate oxidation[12] of the corresponding known sulfide **15**,[13] affords a simple route to the parent heterocycle **4**. Thus, pyrolysis of sulfoxide **2** in the presence of neutral alumina at 160–180° gave, after resublimation, pure naphtho[1,2-c]thiophene (**4**), mp 110–112°, in 47% yield. In contrast to benzo[c]thiophene, the naphtho analog **4** was quite stable to storage at room temperature. Its ultraviolet spectrum showed a complex series of bands (see Experimental Section) which were very similar to those reported[11] for its 1,3-dimethyl derivative **13**.

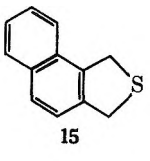
In contrast also to the more reactive thiophene **3**, **4** did not add to NPM at room temperature, but addition did take place at 100° to give a mixture of the exo adduct **16** and the endo adduct **17**. The mixture of adducts **16** and **17** was also conveniently obtained, and in high yield, by refluxing a mixture of acetic anhydride, NPM, and sulfoxide **2**.

The stereochemistry of adducts **16** and **17** was assigned on the basis of their nmr spectra, which were qualitatively similar to those of adducts **8** and **9**. The spectra of **16** and **17** were, however, more complex because of the asymmetric environment in the vicinity of the naphthalene ring. Thus, in the spectrum of exo adduct **16**, the two protons α to the imide carbonyls appear as a sharp singlet at δ 3.43. The bridgehead protons, however, experience deshielding to different degrees by the naphthalene ring and appear as singlets at δ 5.13 and 5.55. The aromatic protons form a complex band in the δ 7.2–8.1 region.

In the endo isomer **17**, the two protons α to the imide carbonyls appear as a multiplet at δ 4.24. Complex splitting results from coupling with the two non-equivalent bridgehead protons, which appear as multiplets centered at δ 5.07 and 5.57. In addition to nine aromatic protons in the δ 6.8–8.1 region, the two protons of the phenyl substituent ortho to the nitrogen atom experience strong shielding by the naphthalene nucleus and appear as a multiplet centered at δ 5.93.



13, R = H
14, R = CO_2H



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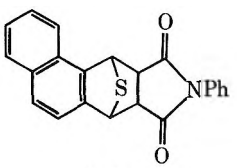


16 (exo)
17 (endo)

(9) In a preliminary communication (ref 1), the absorption at δ 6.43 was assigned incorrectly to the two aromatic protons ortho to the bicyclic ring. The correct assignment became clear upon inspection of the nmr spectra of the corresponding NPM adducts of 1,3-dimethylthieno[3,4-c]thiophene: M. P. Cava and N. M. Pollack, *J. Amer. Chem. Soc.*, **89**, 3639 (1967), and N. M. Pollack, Ph.D. dissertation, Wayne State University, 1968.

(10) R. Meyer, H. Kleinert, S. Richter, and K. Gewald, *J. Prakt. Chem.*, **20**, 244 (1963).

(11) O. Dann and H. Distler, *Chem. Ber.*, **87**, 365 (1954).

(12) N. J. Leonard and C. R. Johnson, *J. Org. Chem.*, **27**, 282 (1962).

(13) M. P. Cava, R. L. Shirley, and B. W. Erickson, *ibid.*, **27**, 755 (1962).

Naphtho[2,3-*c*]thiophene.—Some time ago we reported the synthesis of the deep red 1,3-diphenylnaphtho[2,3-*c*]thiophene (**18**), a remarkably stable substance despite its 2,3-naphthoquinonoid structure.[14] In order to gain some insight into the extent to which the phenyl substituents stabilize this compound, we investigated the synthesis of the parent heterocycle **5** by the sulfoxide dehydration route. Sulfoxide **19**, prepared by the periodate oxidation of the known sulfide **20**,[15] did indeed undergo dehydration to naptho[2,3-*c*]thiophene (**5**) when heated in acetic anhydride in the presence of NPM, as evidenced by the formation of a mixture of adducts in fairly good yield. This mixture was resolved by crystallization and chromatography into a major isomer (A) and two minor isomers (B and C); infrared and tlc examination of the mother liquors failed to reveal the presence of a fourth adduct.

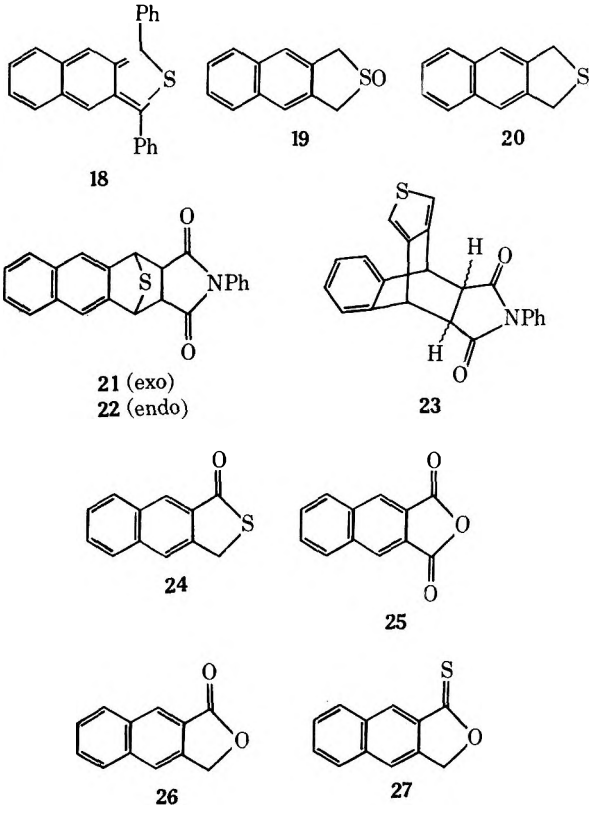
The ultraviolet spectra of adducts A and B are almost identical, each showing absorption up to 330 mμ, consistent with the presence of a naphthalene nucleus. Adducts A and B were formed, therefore, by addition of NPM to the thiophene ring of **5**. The exo configuration **21** was assigned to A on the basis of its nmr spectrum, which revealed the protons α to the imide carbonyls at δ 3.46 and the bridgehead protons at δ 5.13, both sets appearing as sharp singlets. In the nmr spectrum of endo isomer **22** (adduct B), the protons α to the carbonyls appear downfield at δ 4.10, while the bridgehead protons appear at δ 5.05; both signals are multiplets, consistent with the endo configuration. Also, the two phenyl protons ortho to the nitrogen atom in **22** are shielded by the naphthalene nucleus and appear centered at δ 6.08.

Adduct C was assigned structure **23**, in which a molecule of NPM has added to the central ring of **5**. In accord with this formulation, the adduct shows no ultraviolet maxima above 269 mμ. Its nmr spectrum is quite similar to that of the NPM–anthracene adduct **10**.[8] Thus, the protons α to the carbonyls and the bridgehead protons appear as singlets at δ 3.34 and 4.87 respectively, while the two phenyl protons ortho to the nitrogen appear as a shielded multiplet around δ 6.51; the thiophene protons are seen as a sharp singlet at δ 7.06. Unfortunately, these values do not reveal whether the imide ring of **23** lies over the benzene ring or over the thiophene ring.

In an attempt to isolate naphtho[2,3-*c*]thiophene (**5**), sulfoxide **19** was mixed with neutral alumina and heated to 200° under reduced pressure in a sublimer. A thin film of yellow sublimate was obtained on the cold finger, which was maintained at −78°. The sublimate was dissolved in a benzene solution of NPM and the products were analyzed by tlc, revealing the presence of none of the NPM adducts of **5**, but only a small amount of sulfide **20**. Extraction of the alumina residue from the pyrolysis, followed by chromatographic separation, afforded only two products in very low (*ca.* 1%) yield. One product was sulfide **20**; the second product, $C_{12}H_8OS$, was shown to be 1,3-dihydronaphtho[2,3-*c*]thiophen-1-one (**24**). Thiolactone **24** was prepared also by an independent synthesis from 2,3-naphthalic anhydride (**25**) *via* lactone **26** and the isomeric thiolactone **27** as intermediates, as described in detail in the Experimental Section.[16]

It was observed that a solution of sulfoxide **19** in chloroform or ethylene dichloride developed a yellow color and a strong yellow-green fluorescence on heating; a similar color possibly attributable to **5** was produced by the slow passage of a chloroform solution of **19** through a neutral alumina column at room temperature. An attempt to isolate **5** from the column eluate of the latter experiment afforded mostly starting sulfoxide **19** along with smaller amounts of sulfide **20** and thiolactone **24**. In addition, immediate treatment of the yellow eluate with NPM, followed by tlc analysis, failed to give any indication of the presence of adducts of **5**.

Positive evidence was obtained, however, for the slow generation of **5** from **19** in hot ethylene dichloride in the presence of alumina. When a mixture of **19**, NPM, and alumina was heated under nitrogen in ethylene dichloride solution for 24 hr at 85–90°, low yields (*ca.* 6% total) of the NPM adducts of **5** were isolated, along with traces of sulfide **20** and thiolactone **24**.



Discussion

The formation of benzo[*c*]thiophene by the dehydration of sulfoxide **1** may be viewed as a variation of the Pummerer reaction.[17] The sulfonium ion **28** is proposed as an intermediate in this process,[17c] although the acetoxy sulfide **29** may also be involved in acetic anhydride solution.[17b] In the naphtho[2,3-*c*]thiophene case, the intermediate sulfonium ion **30** also is attacked by the nucleophilic oxygen of unchanged sulfoxide **19**; collapse of

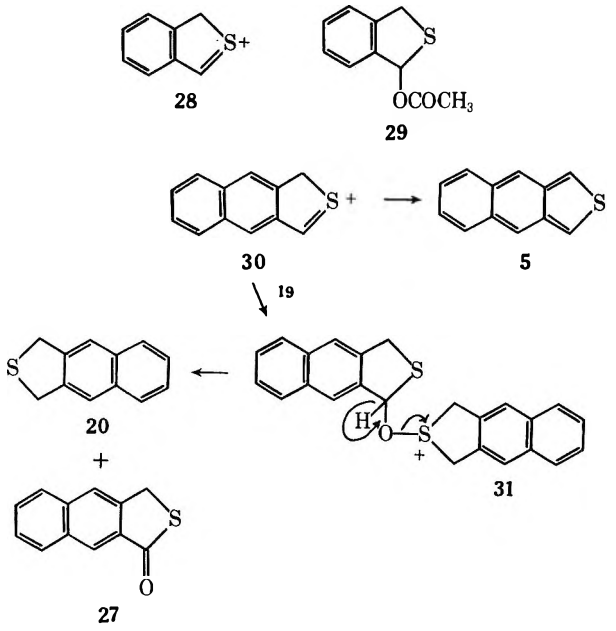
(14) (a) M. P. Cava and J. P. Van Meter, *J. Amer. Chem. Soc.*, **84**, 2008 (1962); (b) *J. Org. Chem.*, **34**, 538 (1969).

(15) M. P. Cava and R. L. Shirley, *J. Amer. Chem. Soc.*, **82**, 654 (1960).

(16) The preparation of related thiophthalides has been reported: (a) V. Prey and P. Kondler, *Monatsh. Chem.*, **89**, 505 (1958); (b) V. Prey, B. Kerres, and H. Berbalk, *ibid.*, **91**, 319 (1960); (c) *ibid.*, **91**, 774 (1960).

(17) (a) L. Horner and P. Kaiser, *Justus Liebigs Ann. Chem.*, **626**, 19 (1959); (b) S. Oae, T. Kitao, S. Kawamura, and Y. Kitaoka, *Tetrahedron*, **19**, 817 (1963); (c) C. R. Johnson, J. C. Sharp, and W. G. Phillips, *Tetrahedron Lett.*, 5299 (1967).

the resulting oxysulfonium ion **31** leads to the observed by-products **20** and **27**. The relative reluctance of ion **30** to lose a proton (as compared to ion **28**) may be attributed to the fact that thiophene **5** is a high-energy 2,3-napthoquinonoid system.[14]



It is of interest to compare the addition of the dienophile NPM to the condensed thiophenes **3**, **4**, and **5**. In all three compounds addition to the thiophene ring was observed; formation of the exo isomer was somewhat favored. Indeed, addition of NPM to a benzenoid ring was observed only in the formation of the minor adduct (**23**) from naphtho[2,3-*c*]thiophene (**5**). Some dienophile addition to the central ring of **5** is not surprising, in view of the fact that **5** is a thiophene analog of anthracene.[18]

Experimental Section

General.—Melting points are uncorrected. Microanalyses were carried out by Midwest Microlab, Inc., Indianapolis, Ind. Spectra were recorded on a Perkin-Elmer Model 137 ir spectrophotometer, a Perkin-Elmer Model 202 uv-visible spectrophotometer, a Varian A-60A nmr spectrometer, and a Perkin-Elmer Model 270B mass spectrometer.

1,3-Dihydrobenzo[*c*]thiophene 2-Oxide (1).[6]—Molten 1,3-dihydrobenzo[*c*]thiophene[3,4] (27.2 g, 0.20 mol) was added dropwise to a stirred solution of 46.0 g (0.215 mol) of sodium periodate in 900 ml of 50% aqueous methanol. After being stirred for 12 hr at room temperature, the reaction mixture was filtered to remove inorganic salts. Evaporation afforded a solid residue which was recrystallized from ethyl acetate–cyclohexane to give 24.2 g (80%) of sulfoxide **1**, mp 85–87°. The analytical sample, mp 90–91°, was recrystallized three times from the same solvent mixture.

Anal. Calcd for C_8H_8OS: C, 63.13; H, 5.29; S, 21.06. Found: C, 63.05; H, 5.38; S, 20.80.

Benzo[*c*]thiophene (3).—An intimate mixture of 2.00 g (13.2 mmol) of 1,3-dihydrobenzo[*c*]thiophene 2-oxide (**1**) and 3.0 g of grade I neutral alumina (Woelm) was heated under 25-mm pressure at 120–130° in a sublimer to give 1.67 g (94%) of benzo[*c*]-thiophene, mp 47–56°, formed during 1 hr as a pure white crystalline solid. An analytical sample, mp 53–55° (lit.[10] mp 50–51°), was prepared by resubliming the crystalline solid at 40–45° (6.0 mm) (15% recovery).

(18) After the submission of our manuscript, an independent study appeared describing the generation of **5** and the isolation of its adducts **21** and **22** (but not **23**): D. W. H. MacDowell, A. T. Jeffries, and M. B. Meyers, *J. Org. Chem.*, **36**, 1416 (1971).

Adducts 8 and 9 of Benzo[*c*]thiophene (3) with *N*-Phenylmaleimide. A. Generation of 3 *in Situ*.—An intimate mixture of 0.456 g (3.00 mmol) of 1,3-dihydrobenzo[*c*]thiophene 2-oxide and 0.692 g (4.00 mmol) of *N*-phenylmaleimide was heated in an oil bath at 220° (vigorous reaction, loss of water). The reaction product was subjected to fractional crystallization to give 0.438 g (48%) of the exo adduct **8**, mp 194–202°, obtained in two crops from benzene. Recrystallization from benzene–ether gave the analytical sample, mp 203–204°.

Anal. Calcd for $C_{18}H_{13}NO_2S$: C, 70.34; H, 4.26; N, 4.56; S, 10.43. Found: C, 70.53; H, 4.36; N, 4.44; S, 10.24.

Fractional crystallization of the residual material obtained by evaporating the mother liquor gave 0.221 g (24%) of the endo adduct **9**, mp 150–190° (from benzene–cyclohexane). Recrystallization from ethanol–ethyl acetate and then from benzene–cyclohexane gave the analytical sample, mp 236–239°.

Anal. Calcd for $C_{18}N_{13}NO_2S$: C, 70.34; H, 4.26; N, 4.56; S, 10.43. Found: C, 70.61; H, 4.36; N, 4.71; S, 10.42.

Similar results were obtained when the reaction was carried out in acetic anhydride. Thus, a mixture of 1.00 g (6.58 mmol) of the sulfoxide **1**, 1.14 g (6.59 mmol) of *N*-phenylmaleimide, and 20 ml of acetic anhydride was heated under reflux for 2 hr and was worked up in the usual way to give 1.75 g (86%) of adduct mixture, mp 170–200°, which was shown by ir analysis to be made up of the exo and endo adducts (**8** and **9**) in the ratio 1.2:1.

B. Use of Pure 3.—Benzo[*c*]thiophene (402 mg, 3 mmol) was added to a solution of 519 mg (3.00 mmol) of *N*-phenylmaleimide and a trace of hydroquinone in 15 ml of benzene. The reaction mixture was allowed to stand at room temperature for 3 days and was then worked up to give a product consisting of the usual ratio of isomers **8** and **9** as shown by tlc and ir analysis.

Adducts 11 and 12 of Benzo[*c*]thiophene (3) with Maleic Anhydride. A. Generation of 3 *in Situ*.—A mixture of 0.610 g (4.00 mmol) of the sulfoxide **1**, 0.390 g (4.00 mmol) of maleic anhydride, and 25 ml of acetic anhydride was heated at reflux for 15 hr. The reaction mixture was evaporated to dryness *in vacuo* and the residue was taken up in benzene and precipitated with ether to give 0.450 g (49%) of crude crystalline product. Recrystallization from benzene–ether afforded 0.225 g (24%) of adduct mixture **11** and **12**, white crystals, mp 148–152° (lit.[10] mp 153–154°).

B. From Pure 3.—A solution of 0.536 g (4.00 mmol) of benzo[*c*]thiophene (**3**), 0.392 g (4.00 mmol) of maleic anhydride, and a trace of hydroquinone in 30 ml of benzene was allowed to stand at room temperature for 12 hr and was then heated under reflux for 1 hr. Evaporation of the reaction mixture and crystallization of the residue from benzene–ether gave 0.419 g (52%) of adduct mixture **11** and **12**, mp 141–155° (lit.[10] mp 153–154°).

1,3-Dihydronaphtho[1,2-*c*]thiophene 2-Oxide (2).—Adding a solution of 7.00 g (32.7 mmol) of sodium periodate in 170 ml of water to a stirred solution of 5.44 g (29.2 mmol) of 1,3-dihydronaptho[1,2-*c*]thiophene (**15**)[13] in 500 ml of ethanol and stirring the reaction mixture for 15 hr at room temperature gave, after the usual work-up (evaporation to half-volume, extraction with benzene, etc.), 3.05 g (52%) of the product, mp 135–142° (crystallized from benzene). Recrystallization from ethyl acetate gave 2.22 g (38%) of pure **2**, mp 141–143°.

Anal. Calcd for $C_{12}H_{10}OS$: C, 71.26; H, 4.98; S, 15.86. Found: C, 71.52; H, 4.84; S, 15.96.

Naphtho[1,2-*c*]thiophene (4).—A mixture of 500 mg (2.48 mmol) of sulfoxide **2** and 800 mg of neutral grade I alumina (Woelm) was heated under 25-mm pressure at 160–180° in a sublimer. After 1 hr, the crude product was scraped from the cold finger and was resublimed at 100° under 25-mm pressure to give 216 mg (47%) of analytically pure naphtho[1,2-*c*]thiophene (**4**): transparent plates; mp 110–112°; ultraviolet spectrum λ_{max}^{MeOH} 208 mμ (log ε 4.45), 223 (4.32), 253 sh (4.38), 257 (4.39), 266 (4.43), 271 (4.53), 277 (4.56), 314 sh (3.78), 318 (3.79), 326 sh (3.71), 332 (3.67), 348 (3.27).

Anal. Calcd for $C_{12}H_8S$: C, 78.20; H, 4.37; S, 17.40. Found: C, 78.15; H, 4.30; S, 17.23.

Adducts 16 and 17 of Naphtho[1,2-*c*]thiophene (4) with *N*-Phenylmaleimide. A. Generation of 4 *in Situ*.—A mixture of sulfoxide **2** (1.010 g, 5.00 mmol) and 0.865 g (5.00 mmol) of *N*-phenylmaleimide in 20 ml of acetic anhydride was heated under reflux for 5 hr. After standing at room temperature for 4 days, the reaction mixture was decanted from a crystalline precipitate of 0.515 g of exo adduct **16**, mp 244–246°. Evapora-

tion of the mother liquor and recrystallization of the resulting residue from benzene–cyclohexane afforded additional product (0.209 g, total 0.724 g, 41%), mp 243–245°. Pure exo adduct, mp 246–247°, was obtained by recrystallization from ethyl acetate–ethanol.

Anal. Calcd for $C_{22}H_{15}NO_2S$: C, 73.93; H, 4.23; N, 3.92; S, 8.97. Found: C, 73.93; H, 4.46; N, 4.01; S, 9.12.

Evaporation of the mother liquors and recrystallization of the residual material from ethanol afforded 0.559 g (31%) of the endo adduct **17**, mp 172–174°. Attempts to obtain a second crop of **17** yielded only an impure mixture of adducts. The analytical sample, mp 174–175°, was recrystallized from ethanol and then from benzene–cyclohexane.

Anal. Calcd for $C_{22}H_{15}NO_2S$: C, 73.93; H, 4.23; N, 3.92; S, 8.97. Found: C, 74.20; H, 4.06; N, 3.87; S, 9.18.

B. Use of Pure 4.—A mixture of 40 mg (0.21 mmol) of **4** and 38 mg (0.22 mmol) of *N*-phenylmaleimide in 10 ml of benzene was heated under reflux for 4 hr. Work-up of the reaction product gave 26 mg (37%) of pure **16**, mp 250–252° (recrystallized from methanol). Tlc and ir analysis of the mother liquor residues showed that they were composed of the usual mixture of **16** and **17**.

1,3-Dihydronaphtho[2,3-*c*]thiophene 2-Oxide (19).—A solution of 1.49 g (8.01 mmol) of 1,3-dihydronaphtho[2,3-*c*]thiophene (**20**)[15] in 350 ml of hot ethanol was mixed with a solution of 1.90 g (8.89 mmol) of sodium periodate in 65 ml of water. The reaction mixture was heated and stirred under reflux for 15 hr. Work-up in the usual way and crystallization from ethyl acetate afforded 1.21 g (75%) of sulfoxide **19**, mp 198–204°. The analytical sample, mp 198–201°, was obtained by recrystallization from ethyl acetate.

Anal. Calcd for $C_{12}H_{10}OS$: C, 71.26; H, 4.98; S, 15.86. Found: C, 71.03; H, 5.15; S, 15.84.

Attempted Preparation of Naphtho[2,3-*c*]thiophene (5) by Dehydration of the Sulfoxide 19 with Alumina. A. At Elevated Temperature.—An intimate mixture of 100 mg (0.50 mmol) of sulfoxide **19** and 200 mg of neutral grade I alumina (Woelm) was heated under 25-mm pressure at 200° in a sublimer provided with a cold finger at −78°. After 10 min the cold finger, which was coated with a thin film of pale yellow sublimate, was dipped into a solution of 100 mg of *N*-phenylmaleimide in 15 ml of benzene. After standing for 1 hr at room temperature, the solution was evaporated to dryness *in vacuo* to give 101 mg of residue. Tlc analysis of the residue showed that adducts **21** and **22** (see below) were not present in detectable quantity; only two spots, corresponding to *N*-phenylmaleimide and the sulfide **20**, could be detected.

The alumina from the attempted preparation of **5** (wt 296 mg) was extracted with methanol–chloroform. Evaporation of the extract *in vacuo* gave 39 mg of an orange glass which was subjected to plc on silica gel (20 × 20 cm plate, 1 mm in thickness) developed twice with benzene. A multiplicity of zones was obtained from which only two products could be isolated, namely 1,3-dihydronaphtho[2,3-*c*]thiophene [**20**, 1.0 mg (*ca.* 1%, purified by sublimation at 90° (0.5 mm), mp 162–164° (lit.[15] mp 169–170°); R_f (0.60 on silica gel eluted with benzene) and ir spectrum identical with those of authentic **20**] and 1,3-dihydronaphtho[2,3-*c*]-thiophen-1-one [**24**, 0.6 mg (<1%); R_f (0.27 on silica gel eluted with benzene) and ir spectrum identical with those of authentic **24** (see preparation below)].

B. At Room Temperature.—A solution of 0.050 g (0.25 mmol) of sulfoxide **19** in *ca.* 0.25 ml of alcohol-free chloroform was passed through a small column of alumina (1.5 g of neutral grade I Woelm alumina, column dimensions: diameter, 1 cm; length, 1.5 cm). The column was eluted first with 20 ml of alcohol-free chloroform (prepared by passing reagent grade chloroform through 25 g of neutral grade I alumina), and then with 25 ml of 3% methanol–chloroform. The eluate was evaporated to a small volume and was subjected to plc on one 20 × 20 cm silica gel plate (1 mm thickness) to give a number of zones, from which only three compounds could be isolated in appreciable amounts, namely the starting material [**19**, 0.036 g (72% recovery)], 1,3-dihydronaphtho[2,3-*c*]thiophene [**20**, 0.004 g (31% yield, based on unrecovered starting material), purified by sublimation, mp 162–165° (lit.[15] mp 169–170°), R_f and ir spectrum identical with those of authentic material], and 1,3-dihydronaphtho[2,3-*c*]thiophen-1-one [**24**, 0.0005 g (3.5% yield, based on unrecovered starting material), R_f and ir spectrum identical with those of authentic **24** (see preparation below)].

Adducts 21, 22, and 23 of Naphtho[2,3-*c*]thiophene (20) with *N*-Phenylmaleimide. A. Generation of 20 by Dehydration of the Sulfoxide 19 with Acetic Anhydride.—A mixture of 3.20 g (16.0 mmol) of sulfoxide **19**, 3.0 g (17.0 mmol) of *N*-phenylmaleimide, and 20 ml of acetic anhydride was heated under reflux for 4 hr. After standing at room temperature for 12 hr, the reaction mixture was decanted from a crystalline precipitate; recrystallization of this material from ethyl acetate–chloroform gave 1.7 g (30%) of pure exo adduct **21**, mp 279–282°, and an impure second crop, 0.20 g (4%), mp 275–281°. The analytical sample of **21**, mp 280–282°, was recrystallized from ethyl acetate.

Anal. Calcd for $C_{22}H_{15}NO_2S$: C, 73.93; H, 4.23; N, 3.92; S, 8.97. Found: C, 73.93; H, 4.46; N, 4.01; S, 9.12.

Evaporation of the acetic anhydride mother liquors (see above) afforded a solid residue which was recrystallized from benzene–ether to give 1.10 g (19%) of endo adduct **22**, mp 190–205°. Repeated recrystallization of this material from ethyl acetate and benzene–cyclohexane gave the analytical sample (0.30 g, 5%), mp 212–215°.

Anal. Calcd for $C_{22}H_{15}NO_2S$: C, 73.93; H, 4.23; N, 3.92; S, 8.97. Found: C, 73.96; H, 4.40; N, 4.08; S, 9.19.

The mother liquors from the crystallization of **22** were concentrated to a small volume and diluted with ether to give 0.30 g (5%) of crude adduct **23**, mp 215–235°, which was recrystallized alternately from ethyl acetate and benzene–cyclohexane to give the analytical sample (0.13 g, 2%), mp 243–246°.

Anal. Calcd for $C_{22}H_{15}NO_2S$: C, 73.93; H, 4.23; N, 3.92; S, 8.97. Found: C, 74.13; H, 4.47; N, 4.15; S, 9.02.

When the work-up of the adducts was carried out by plc instead of by fractional crystallization, the yields of **21** and **22** were improved. Thus, heating 0.202 g (1.00 mmol) of sulfoxide **19**, 0.173 g (1.00 mmol) of *N*-phenylmaleimide, and 2.0 ml of acetic anhydride in a sealed tube under nitrogen for 3 hr at 145°, followed by the usual preliminary crystallization, afforded 0.111 g crude exo adduct **21**, which was recrystallized from chloroform–ethyl acetate to give 0.077 g of pure material, mp 281–281.5°, obtained in two crops. Evaporation of the combined mother liquors gave 0.269 g of residue which was chromatographed on two 20 × 40 × 0.2 cm silica gel plates (E. Merck) developed four times with 0.25% methanol in benzene. Elution of the resulting zones and crystallization of the solid material so obtained gave an additional 0.056 g of **21**, mp 281–282° (total yield, 0.133 g, 37.3%), and 0.040 g (11.2%) of **22**, mp 214–215°. The purity of the **23** obtained by plc work-up (0.028 g, 7.8%, mp 219–221°) was inferior to that obtained by fractional crystallization (see above).

B. Generation of 20 by Dehydration of the Sulfoxide 19 with Alumina.—A mixture of 0.101 g (0.5 mmol) of sulfoxide **19**, 0.087 g (0.5 mmol) of *N*-phenylmaleimide, 0.050 g of neutral grade I alumina (Woelm), and 3 ml of ethylene dichloride was heated in a sealed tube under nitrogen at 85–90° for 24 hr. Preparative layer chromatographic separation of the product mixture on one 20 × 20 cm silica gel plate (Merck, 2-mm thickness), eluted twice with benzene, gave the three adducts, **21** [0.008 g (4.5%), mp 280.5–281° (recrystallized from chloroform–ethyl acetate)], **23** [trace amount; R_f identical with that of authentic **23**], and **22** [0.003 g (1.7%), mp 191–198° (recrystallized from chloroform–ethyl acetate)], together with trace quantities of 1,3-dihydronaphtho[2,3-*c*]thiophene (**20**) and 1,3-dihydronaphtho[2,3-*c*]thiophen-1-one (**24**).

1,3-Dihydronaphtho[2,3-*c*]furan-1-one (26).—A suspension of 40.0 g (0.20 mol) of naphthalene-2,3-dicarboxylic anhydride (**25**) and 10.0 g (0.26 mol) of sodium borohydride in 1 l. of THF was boiled under reflux for 15 min. The reaction mixture was evaporated to dryness *in vacuo* and the solid residue was dissolved in 500 ml of ice water. Acidification with dilute hydrochloric acid gave a crystalline precipitate which was mixed with xylene and heated for 2 hr to complete the lactonization. Addition of pentane and cooling gave a crystalline solid which was recrystallized from THF to give 30.0 g (80%) of pure **26**, mp 207–209°.

Anal. Calcd for $C_{12}H_8O_2$: C, 78.25; H, 4.38. Found: C, 78.33; H, 4.37.

1,3-Dihydronaphtho[2,3-*c*]furan-1-thione (27).—A suspension of 11.1 g of phosphorus pentasulfide and 9.2 g (0.05 mol) of lactone **26** in xylene was refluxed for 2 hr. The reaction mixture was filtered while hot and the filtrate was evaporated to dryness *in vacuo*. Recrystallization of the residue from THF gave an orange precipitate which was chromatographed on a column of silica gel with 1:1 benzene–cyclohexane to give 4.25 g (45%) of

the thiolactone **27**, mp 192–193°. The analytical sample was recrystallized from benzene, mp 194–195°.

Anal. Calcd for $C_{12}H_8OS$: C, 71.97; H, 4.02; S, 16.01. Found: C, 71.93; H, 4.09; S, 15.83.

1,3-Dihydronaphtho[2,3-c]thiophen-1-one (24).—A mixture of 0.100 g (1.00 mmol) of 1,3-dihydronaphtho[2,3-c]furan-1-thione (**27**) and 1.8 ml of pyridine was heated under nitrogen in a sealed tube at 190° for 8 hr. The reaction mixture was diluted with chloroform, washed with dilute aqueous hydrochloric acid, dried over magnesium sulfate, and evaporated to dryness *in vacuo*. Recrystallization of the residue from benzene gave 0.072 g (72%) of the product, mp 174–175°, obtained in two crops.

Anal. Calcd for $C_{12}H_8OS$: C, 71.97; H, 4.02; S, 16.01. Found: C, 71.85; H, 4.30; S, 15.84.

The product was also obtained when quinoline was used as the solvent but in lesser yield and poorer quality.

Registry No.—**1**, 3533-72-0; **2**, 31739-49-8; **3**, 270-82-6; **4**, 232-81-5; **8**, 13129-12-9; **9**, 13129-13-0; **11**, 31736-38-6; **12**, 31790-98-4; **16**, 13129-15-2; **17**, 13129-16-3; **19**, 28238-02-0; **21**, 31736-40-0; **22**, 31736-41-1; **23**, 31739-52-3; **24**, 31739-53-4; **26**, 4711-50-6; **27**, 31739-55-6.

Acknowledgment.—We thank the National Science Foundation for a grant in support of this research.

The Synthesis, Properties, and Base-Catalyzed Interactions of 8-Substituted 6,7-Dimethyllumazines[1]

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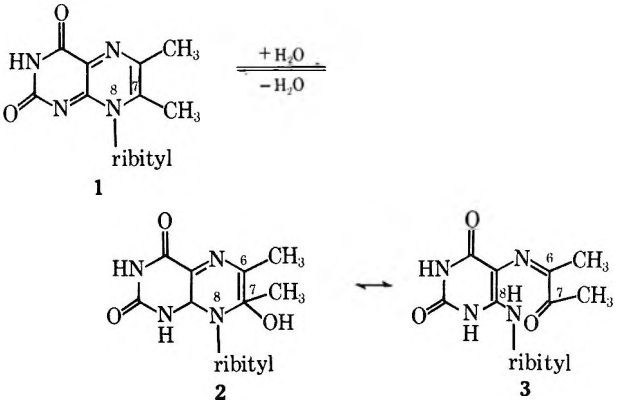
Received March 25, 1971

Alkaline solutions of 6,7-dimethyllumazines substituted at position 8 with groups bearing a 2′-hydroxyl group exhibit no long wavelength absorption; analogs without a 2′-hydroxyl group show absorption in the visible range. In H_2O, at alkaline pH, analogs with a 2′-hydroxyl substituent show nmr absorption of the 7-methyl group at −1.37 ppm, while the 6-methyl group exhibits singlets at −2.17 and −2.07 ppm. Analogs lacking the 2′-hydroxyl group do not absorb at −1.37 ppm but exhibit two resonance peaks between −3.90 and −4.30 ppm and a single absorption peak of the 6-methyl group at −2.07 ppm. These data suggest that 8-substituted 6,7-dimethyllumazines which bear a 2′-hydroxyl group form an equilibrium mixture in alkaline solutions containing primarily an intramolecular ether formed between the 2′-hydroxyl group of the side chain at position 8 and carbon 7 of the pyrazine ring (7-methyl group at −1.37 ppm, 6-methyl group at −2.17 ppm) and a minor amount of the 7-exo methylene form (6-methyl group at −2.07 ppm). Without a 2′-hydroxyl on the group at position 8, the intramolecular ether cannot form and the 7-exo methylene form predominates in basic media. The synthesis and properties of eight new 6,7-dimethyllumazine derivatives bearing D- and L-erythrityl, D- and L-threityl, 2′-deoxy-D-ribityl, DL-glyceryl, and 3′-hydroxypropyl substituents at position 8 and their corresponding 4-(1′-alditylamino)-5-nitroso-2,6-dihydroxypyrimidine precursors are reported. The preparation and characterization of the oximes of D- and L-erythrose, D- and L-threose, 2-deoxy-D-ribose, 3-deoxy-D-ribose, and the corresponding amines formed by reduction are described. These syrupy amines are characterized as their crystalline salicylidene derivatives.

The mechanism for conversion of 6,7-dimethyl-8-ribityllumazine to riboflavin chemically[3–7] and enzymically[8,9] has been studied in some detail over the past decade. It was thought originally that the conversion occurred by an aldol condensation involving an α-methyl ketone resulting from hydration and ring opening of the pyrazine ring.[3,5]

More recent work strongly suggests a 7-exo methylene intermediate **7** described below[6–9] rather than the α-methyl ketone **3**. Pfleiderer[10] has interpreted the spectra of alkaline solutions of various lumazines as evidence of hydration and the ring-opening reaction sequence. This report presents nuclear magnetic resonance data substantiating the presence of the 7-exo methylene (**7**) structure and the absence of the open ring (**3**) form in basic solution.



Nuclear magnetic resonance spectra of a number of selected and newly synthesized 6,7-dimethyllumazines substituted at position 8 with various groups indicate that, if the substituent at position 8 bears a 2′-hydroxyl group, an equilibrium mixture results. This is predominantly an intramolecular ether resulting from the base-catalyzed interaction of the 2′-hydroxy group and carbon 7 of the pyrazine ring, with a minor amount of 7-exo methylene form which may result from either the addition of hydroxide ion from the solvent to carbon 7

(1) A preliminary report was presented at the 106th National Meeting of the American Chemical Society, Chicago, Ill., Sept 13–18, 1970. Supported in part by a grant from the National Institute of Arthritis and Metabolic Diseases (AM10501 and AM15404), U. S. Public Health Service.

(2) The data presented in this publication were derived from a Ph.D. Thesis by R. L. Beach submitted to Rutgers University, 1970. Summaries of more detailed results can be obtained from this author upon request.

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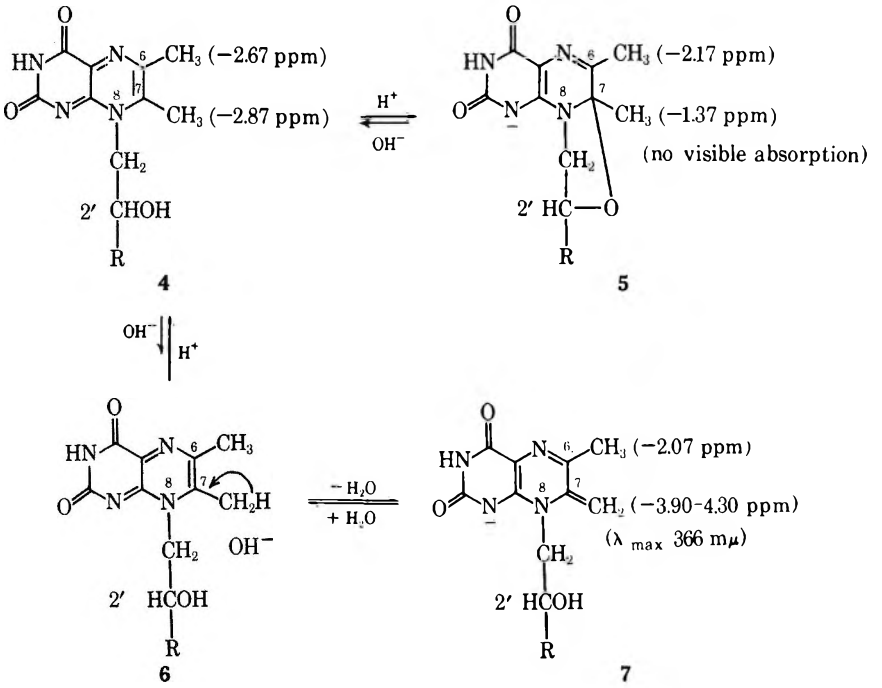

of the pyrazine ring (2), followed by an elimination reaction, or by direct proton abstraction.

If the substituent at position 8 lacks the 2′-hydroxyl group, the predominant form is that of the 7-exo methylene (7) since the intramolecular ether can *only* be formed through interaction of the 2′-hydroxyl group and carbon 7 of the pyrazine ring.

The phenomena outlined above explain the apparent confusion in the literature with respect to the absorption spectra in basic solution of 6,7-dimethyl-8-substituted lumazines. It has been shown that 6,7,8-trimethyllumazine,[11] 6,7-dimethyl-8-(2′-hydroxyethyl)-lumazine,[12] and 6,7-dimethyl-8-ethyllumazine[12] exhibit long wavelength absorption in basic solution, while the 6,7-dimethyllumazines bearing alditol substituents[13] at position 8 do not exhibit long wavelength absorption. The long wavelength absorption can now be attributed to the presence of the 7-exo methylene form (7); the absence of long wavelength absorption indicates the intramolecular ether form (5) predominant when the alditol substituent bears the 2′-hydroxyl group. A similar lack of long wavelength absorption has been shown by Hemmerich and Wood[14] when various nucleophiles are added to the 7-carbon of the lumazine nucleus.

Experimental Section

Materials.—The following materials were purchased from the suppliers indicated: 2,4-dimethoxy-6-chloropyrimidine, 2-deoxy-D-ribose, 3-amino-1-propanol, 3-amino-1,2-propanediol (Aldrich); 2,3-butanedione (Fisher Scientific); Dowex AG-1 X 10 (minus 400 mesh), Dowex AG-50W X 12 (200–400 mesh) (Bio-Rad); platinum oxide (American Platinum Works of Newark); deuterium oxide (99.7%) (Mallinckrodt); deuterium oxide with 1% DSS[15] (Merck Sharp and Dohme). All other compounds were of reagent quality.

The following compounds were prepared by the methods indicated: **2,4-Dihydroxy-6-chloropyrimidine,**[11] mp 300–302° (lit. 301–302°); **D-erythrose,**[16] $[\alpha]^{25}D$ −25° (lit. −32°); **D-threose,**[16] $[\alpha]^{25}D$ +10° (lit.[17] +12°), mp 24–28° (lit. 24–30°); **L-erythrose,**[17] $[\alpha]^{25}D$ +22° (lit. +39°); **1,3-*O*-benzylidene-L-arabinitol;**[18] **2,4-*O*-benzylidine-L-threose hemihydrate,**[19] mp 115–119° (lit. 119–120°); **L-threose,**[19] $[\alpha]^{25}D$ −11°; **methyl 3-deoxy-β-D-ribofuranoside;**[20] **6,7-dimethyl-8-(1′-D-ribityl)lumazine,**[11] λ_{max} 407 mμ (ε 10,500) [lit. λ_{max} 407 mμ (ε 10,300) in 0.1 *N* H_2SO_4]; **6,7-dimethyl-8-(2′-hydroxyethyl)lumazine,**[21] λ_{max} 407, 225 mμ, λ_{min} 275 mμ (lit. λ_{max} 407, 256 mμ, λ_{min} 270 mμ in 0.1 *N* H_2SO_4); **6,7,8-trimethyllumazine,**[22] λ_{max} 407, 275, 256 mμ (lit. λ_{max} 408, 274, 256 mμ in 0.1 *N* H_2SO_4).

3-Deoxy-D-ribose.—Methyl 3-deoxy-β-D-ribofuranoside (2.4 g) in 60 ml of 1.0 *N* H_2SO_4 was heated on a steam bath for 1 hr. The solution was cooled, neutralized with exchange resin AG-1 X 10 (bicarbonate form), and filtered. The resin was washed with two 25-ml portions of water, the washings were combined with the main solution, and the solvent was removed under reduced pressure at 25°, yielding 2.1 g of 3-deoxy-D-ribose as a pale yellow syrup.

Oximes. D- and L-erythrose, D- and L-threose, 2-deoxy-D-ribose, and 3-deoxy-D-ribose were converted to their respective oximes by the method of Winestock and Plaut.[13] Only 2-deoxy-D-ribose oxime was obtained crystalline from absolute ethanol, mp 95–96°. *Anal.* Calcd for $C_5H_{11}NO_4$: C, 40.26; H, 7.44. Found: C, 40.36; H, 7.50. The nmr spectra of aldose oximes are reported elsewhere.[2]

Alditylamines.—Various aldose oximes were suspended in glacial acetic acid and reduced at room temperature over PtO_2 in a Parr hydrogenation apparatus at an initial hydrogen pressure of 50 lb/in^2. The amines were purified on columns of AG-50W X 12 as described by Winestock and Plaut.[13] Nmr spectra of individual amines are reported elsewhere.[2]

Salicylidene Derivatives of Alditylamines.—The alditylamines, isolated as syrups, were characterized further as crystalline salicylidene derivatives as follows. Salicylaldehyde (0.5 ml) was added to each alditylamine (2 mmol) dissolved in 50 ml of absolute ethanol. The resulting yellow solution was heated for 30 min at 80° and left overnight at room temperature. The solvent was removed under reduced pressure at 35°, and the yellow residue was triturated with two 5-ml portions of diethyl ether

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TABLE I

LIGHT ABSORPTION SPECTRA OF 6,7-DIMETHYL-8-(1′-ALDITYL)LUMAZINES

8-(1′-Alditol) groups	Registry no.	0.1 N H_2SO_4 λ_{max}	ϵ	λ_{min}	ϵ	0.1 N NaOH λ_{max}	ϵ	λ_{min}	ϵ
D-Threityl	31735-28-1	407	1.01×10^4	300	8.40×10^2	313	9.55×10^3	292	6.55×10^3
		256	1.48×10^4	225	8.06×10^3	279	1.20×10^4	255	7.91×10^3
						277	2.22×10^4		
L-Threityl	31735-29-2	407	1.04×10^4	300	8.62×10^2	313	1.05×10^4	292	7.47×10^3
		256	1.50×10^4	225	8.21×10^3	279	1.27×10^4	255	9.11×10^3
						227	2.38×10^4		
D-Erythrityl	31735-30-5	407	9.99×10^3	300	8.11×10^2	313	6.91×10^3	292	5.08×10^3
		256	1.18×10^4	225	7.72×10^3	279	9.89×10^3	255	6.39×10^3
						227	1.84×10^4		
L-Erythrityl	31735-31-6	407	9.95×10^4	300	4.68×10^2	313	6.66×10^3	292	4.85×10^3
		256	1.37×10^4	225	6.34×10^3	279	9.48×10^3	255	5.69×10^3
						227	1.72×10^4		
2′-Deoxy-D-ribityl	31735-32-7	407	1.05×10^4	300	2.24×10^3	366	3.48×10^3	290	7.78×10^3
		256	1.24×10^4	225	6.66×10^3	313	1.63×10^4	262	7.09×10^3
						282	8.33×10^3		
						235	1.77×10^4		
3′-Deoxy-D-ribityl	31735-33-8	407	1.07×10^4	300	8.81×10^2	313	9.63×10^3	292	7.41×10^3
		256	1.45×10^4	225	8.13×10^3	280	1.21×10^4	255	8.89×10^3
						228	2.25×10^4		
3′-Hydroxypropyl	31735-34-9	407	1.07×10^4	300	3.72×10^2	365	4.76×10^3	335	4.40×10^3
		275	9.80×10^3	270	9.53×10^3	313	1.90×10^4	275	6.67×10^3
		256	1.34×10^4	225	6.70×10^3	265	6.74×10^3	262	6.63×10^3
						235	1.50×10^4		
DL-Glyceritol	31790-90-6	407	1.06×10^4	300	3.43×10^2	313	1.00×10^4	292	7.11×10^3
		256	1.39×10^4	225	6.54×10^3	279	1.12×10^4	255	7.41×10^3
						227	2.01×10^4		

leaving a thick yellow syrup. The residue was dissolved in 10 ml of hot absolute ethanol and hexane was added until the solution became cloudy. The solution was allowed to cool to room temperature, yielding a yellow crystalline solid which may be recrystallized from benzene. The melting points of the derivatives were as follows: D-threitylamine, 74–76°; D-erythritylamine, 84–86°; L-erythritylamine, 86–87°; 2-deoxy-D-ribitylamine, 76–77°; D-ribitylamine, 121–123°. The derivatives had the following absorption characteristics: in 0.1 *N* HCl, maxima at 274–279 and 345 mμ and minima at 238–240 and 303 mμ; in 0.1 *N* NaOH, maxima were at 223–227, 263–265, 375 mμ, and minima at 248–250 and 295 mμ. Molar absorbancies at these wavelengths have been recorded.[2]

4-(1′-Alditylamino)-5-nitroso-2,6-dihydroxypyrimidine.—These compounds were prepared according to the method of Plaut.[23] The absorption properties of these compounds are similar to those of analogous substances reported previously;[13] yields, analytical data, and decomposition points are recorded elsewhere.[2]

6,7-Dimethyl-8-(1′-alditol)lumazines.—Reduction of specific 4-(1′-alditylamino)-5-nitroso-2,6-dihydroxypyrimidines with sodium hydrosulfite and condensation of the resulting diamine with 2,3-butanedione according to the procedure of Winestock and Plaut[13] yielded the corresponding 6,7-dimethyllumazines selectively substituted with various alditol groups at position 8.

The light absorption spectra of the compounds are summarized in Table I and Figures 1 and 2. Nmr spectra in neutral solutions were similar to analogous compounds described previously.[9] Details of nmr spectra, decomposition points, yields, and analytical data have been recorded elsewhere.[2]

Methods.—Melting or decomposition points were determined in a Thomas-Hoover capillary melting point apparatus and are uncorrected. Ultraviolet and visible spectra were recorded in a Cary Model No. 14 spectrophotometer. Microanalysis was done by Mr. George I. Robertson of Florham Park, N. J. Nuclear magnetic resonance spectra were measured in a Varian A-60A spectrometer using 1.5% solutions of each compound in D_2O (99.7%) containing 0.25% DSS as an internal standard absorbing at 0.00 ppm. All chemical shifts are reported in parts per million (ppm) shifted downfield from the internal standard assigned a chemical shift of 0.00 ppm.

Nmr Spectra (Figures 3 and 5).—The following conditions were used to determine the spectra shown. Figure 5: (a) A solution of each compound (7.5 mg) in 0.45 ml of D_2O, (b) was made alkaline with 0.05 ml of 1.0 *M* NaOD, (c) followed by neutralization with 0.05 ml of 1.0 *M* DCl. The conditions described in Figure 3 (A, B, and C) were identical with those under Figure 5 (a–c) except that the solvent was H_2O. An internal standard of 0.25% DSS was present in all solutions.

(23) G. W. E. Plaut, *J. Biol. Chem.*, **238**, 2225 (1963).

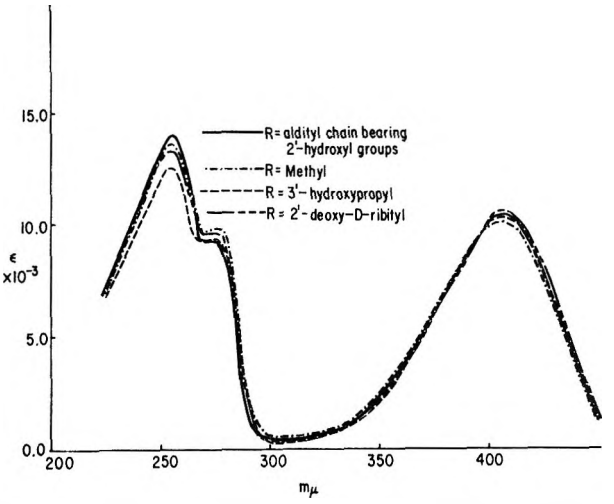


Figure 1.—Absorption spectra in 0.1 *N* H_2SO_4 of 6,7-dimethyllumazines with varying substituents at position 8.

Results and Discussion

Spectroscopy.—Winestock and Plaut[13] have noted that a number of 6,7-dialkyl-8-substituted lumazines show very similar ultraviolet and visible light absorption in *acid media*, typically exhibiting maxima at 407 and 256 mμ and minima at 300 and 225 mμ. Similar characteristics of light absorption have been obtained with the newly synthesized lumazines (Table I and Figure 1).

It has been observed previously[10,11,13,21] that in alkaline media a number of 6,7-alkyl-8-substituted

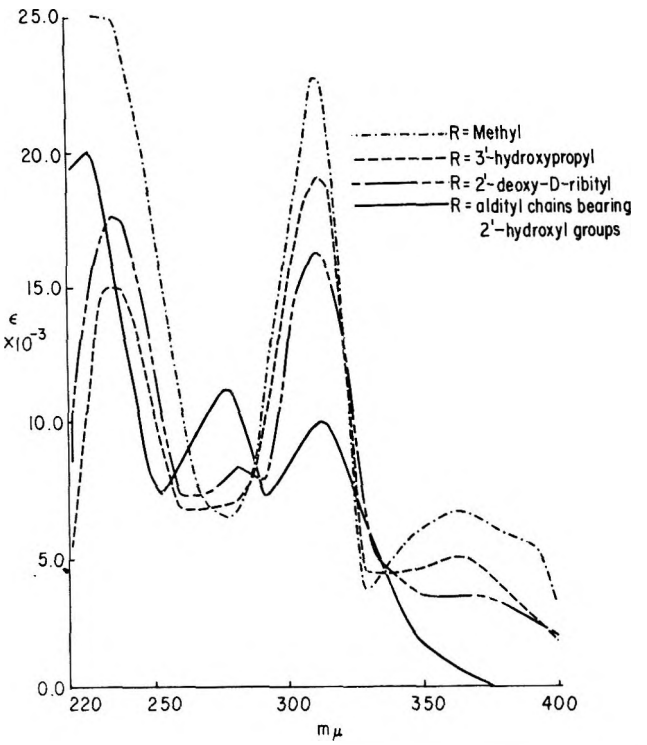


Figure 2.—Absorption spectra in 0.1 *N* NaOH of 6,7-dimethyllumazines with varying substituents at position 8.

lumazines (*e.g.*, compounds bearing tetrahydroxypentyl and pentahydroxyhexyl groups at position 8) and the new compounds (Table I) excepting 6,7-dimethyl-8-[1′-(2′-deoxy-D-ribityl)]lumazine and 6,7-dimethyl-[1′-(3′-hydroxypropyl)]lumazine exhibit no absorption in the visible region but do absorb in the ultraviolet region with maxima at 313, 279, and 227 mμ (Figure 2). Under alkaline conditions a number of other lumazine derivatives (*e.g.*, 6,7,8-trimethyllumazine,[13] 6,7-dimethyl-8-(2′-hydroxyethyl)lumazine,[12] and the new compounds, 6,7-dimethyl-8-[1′-(2′-deoxy-D-ribityl)]lumazine and 6,7-dimethyl-8-[1′-(3′-hydroxypropyl)]lumazine, Table I and Figure 2) retain absorption in the visible range (360–400 mμ) with a maximum in the vicinity of 366 mμ. The only structural difference between compounds with visible absorption in alkaline solution and those without is the absence and presence, respectively, of a 2′-hydroxyl group on the substituent at position 8. 6,7-Dimethyl-8-[1′-(2′-hydroxyethyl)]lumazine deviates from this pattern, and an explanation is offered later for its apparent aberrant spectral properties.

Loss of absorption in the visible range of the spectrum was demonstrated by Hemmerich and Wood[14] when nucleophiles were added at position 7 of lumazine derivatives. Hydroxylation at carbon 7 similarly results in the loss of absorption in the visible range of the spectrum.[10] The absorption at long wavelength of 6,7,8-trimethyllumazine and 6,7-dimethyl-8-(2′-hydroxyethyl)lumazine in 0.1 *N* NaOH[10,11,13] (Figure 2) disappears upon reduction leading to formation of 1,7-dihydro-6,7,8-trimethyllumazine[24] and 7,8-dihydro-6,7-dimethyl-8-(2′-hydroxyethyl)lumazine.[14] This suggests that covalent bond formation between carbon 7 and another group, be it a nucleophile or hydrogen, causes loss of visible absorption.

(24) J. M. McAndless and R. Stewart, *Can. J. Chem.*, **48**, 263 (1970).

In basic solution the 2′-hydroxyl group, therefore, appears to act as the preferred nucleophile and covalently bonds with carbon 7 of the pteridine ring, forming an intramolecular ether **5** and resulting in abolition of visible absorption. With analogs lacking a 2′-hydroxyl group, hydroxide ion from solution may add to carbon 7 of the pteridine ring, as suggested by Cresswell and Wood,[3] Rowan and Wood,[4,5] and Pfleiderer,[10] and depicted as structure **2**. If this intermediate is present, it must be in low concentration since its formation would also result in the abolition of visible absorption. Since visible absorption is observed, an alternate mechanism (**4**–**7**) involving the direct abstraction of proton from the 7-methyl group by solvent hydroxide ion (**6**) is suggested, leading directly to the 7-exo methylene intermediate **7** which absorbs in the visible region of the spectrum. It will be shown that the nmr data in Figures 3–5 are consistent with a direct elimination rather than hydration followed by elimination.

Nuclear Magnetic Resonance Spectroscopy. Analog with a 2′-Hydroxyl Group at the Substituent at Position 8.—6,7-Dimethyllumazines which are substituted at position 8 with groups bearing a 2′-hydroxyl group (Figure 3, I and II) as well as the D-ribityl,[25] D- and L-erythrityl, and D- and L-threityl analogs (spectra not included since they are virtually indistinguishable from those in Figures 3, I and II) exhibit significant absorption at −1.37 ppm in basic H_2O. The loss of long wavelength (visible) absorption in 0.1 *N* NaOH is attributable to covalent bond formation between a nucleophilic group and carbon 7. It appears that the chemical shift to −1.37 ppm for the 7-methyl group similarly arises because of the change in the electronic environment in the vicinity of the 7-methyl group caused by the formation of a covalent bond at carbon 7.

The chemical shifts of 6,7-dimethyl-8-ribityllumazine and 6-deuteriomethyl-7-methyl-8-ribityllumazine in neutral and basic solution have been previously reported by the authors.[25] The assignments of the chemical shifts were based upon the fact that the 7-methyl group exhibits hydrogen–deuterium exchange, slowly in neutral D_2O and very rapidly in basic D_2O. Furthermore, absorption in the vicinity of −2.10 ppm in alkaline solution is due to the 6-methyl group, since absorption in this region is observed with 6,7-dimethyl-8-ribityllumazine but not with 6-deuteriomethyl-7-methyl-8-ribityllumazine.[25] The chemical shift assignments and the exchange phenomena are in accord with those found concurrently by Paterson and Wood[6] and later by McAndless and Stewart.[25] The chemical shift of −1.37 ppm is assigned to the 7-methyl group of the intramolecular ether form **5** in which the 2′-hydroxyl group is acting as the nucleophile covalently bound to carbon 7 of the pteridine ring. The compounds [V (276) and V (344)] below reported in the Varian NMR Spectra Catalog[26] exhibit methyl groups in a similar electronic environment and exhibit equivalent chemical shifts.

Further proof that the absorption at −1.37 ppm is properly assigned to the 7-methyl group is obtained by neutralizing the basic H_2O solutions with 1 equiv of

(25) R. L. Beach and G. W. E. Plaut, *Biochemistry*, **9**, 760 (1970).

(26) "NMR Spectra Catalog," Varian Associates. Vol. 1 and 2, 1962–1963.

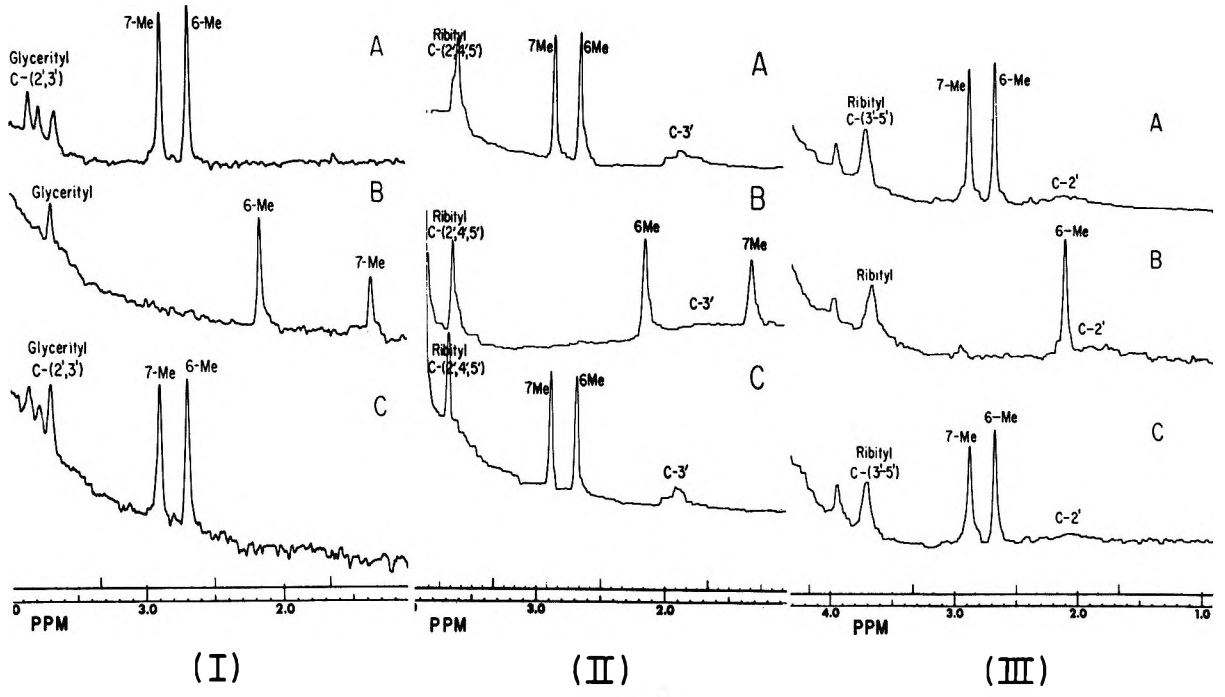
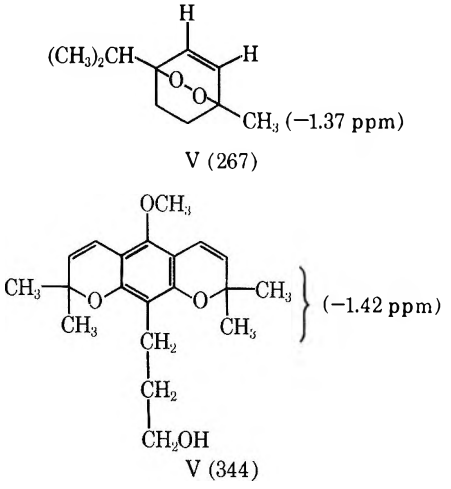


Figure 3.—Nmr spectra of 6,7-dimethyl-8-[1′-(DL-glycerityl)]lumazine (I), 6,7-dimethyl-8-[1′-(3-deoxy-D-ribityl)]lumazine (II), and 6,7-dimethyl-8-[1′-(2′-deoxy-D-ribityl)]lumazine (III) in H_2O: A, compounds in water; B, in 0.1 *N* NaOH; C, B brought to neutrality with 0.1 *N* HCl. The spectra of I and II were recorded at 37°; III was determined at 7°. Other conditions are described under Methods.



HCl (Figure 3C, I and II). The original spectra of the lumazine analogs in neutral solution (*cf.* Figure 3A, I and II) reappear and absorption at −2.87 ppm (7-methyl group[25]) is present. When observations of nmr spectra of 6,7-dimethyllumazines containing the 2′-hydroxyl group (*e.g.*, as shown in Figure 3, I and II) were done in D_2O under conditions where hydrogen–deuterium exchange equilibrium occurred, absorption peaks attributable to the 7-methyl group disappeared.[2,25]

The fact that the 7-methyl group is capable of rapid hydrogen–deuterium exchange in basic D_2O suggests that there is an equilibrium between the intramolecular ether **5** and the 7-exo methylene forms **7**. If the molecules were totally in the intramolecular ether form **5**, hydrogen–deuterium exchange could not occur. Two observations support the occurrence of these two forms, **5** and **7**, in alkaline solution. First, the absorption intensity at −1.37 ppm (7-methyl group of the ether form) is only about 75% of that in the vicinity of −2.10

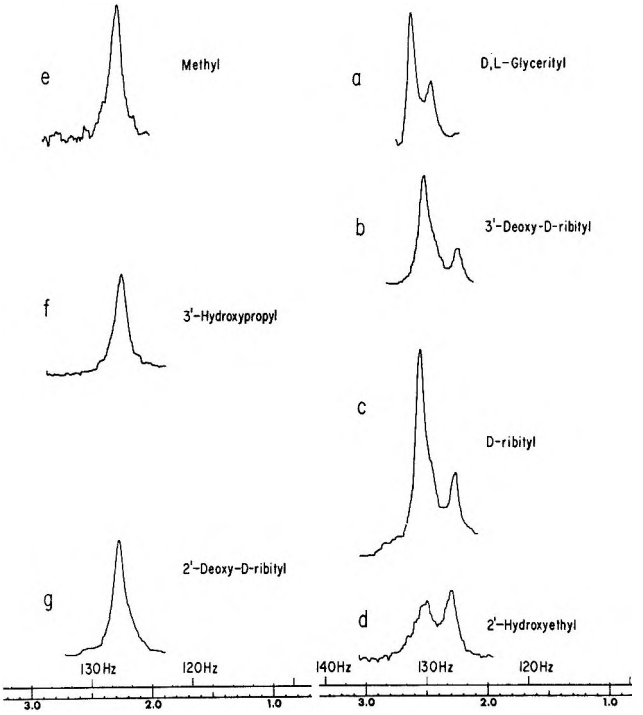


Figure 4.—Nmr spectra of the 6-methyl group of various 6,7-dimethyl-8-substituted lumazines in 0.1 *N* NaOH at 37°.

ppm (6-methyl group)[25] indicating that only 75% of the molecules are in the ether form. Secondly, the 6-methyl group should exhibit two different chemical shifts since the electronic environment of the 6-methyl group in the ether form **5** is different from that in the 7-exo methylene form **7**.

Scale expansion (Figure 4a–d) shows that the absorption at −2.10 ppm is composed of two singlets, one at −2.17 ppm and the other at −2.07 ppm. The intensities of absorption at −1.37 ppm (7-methyl

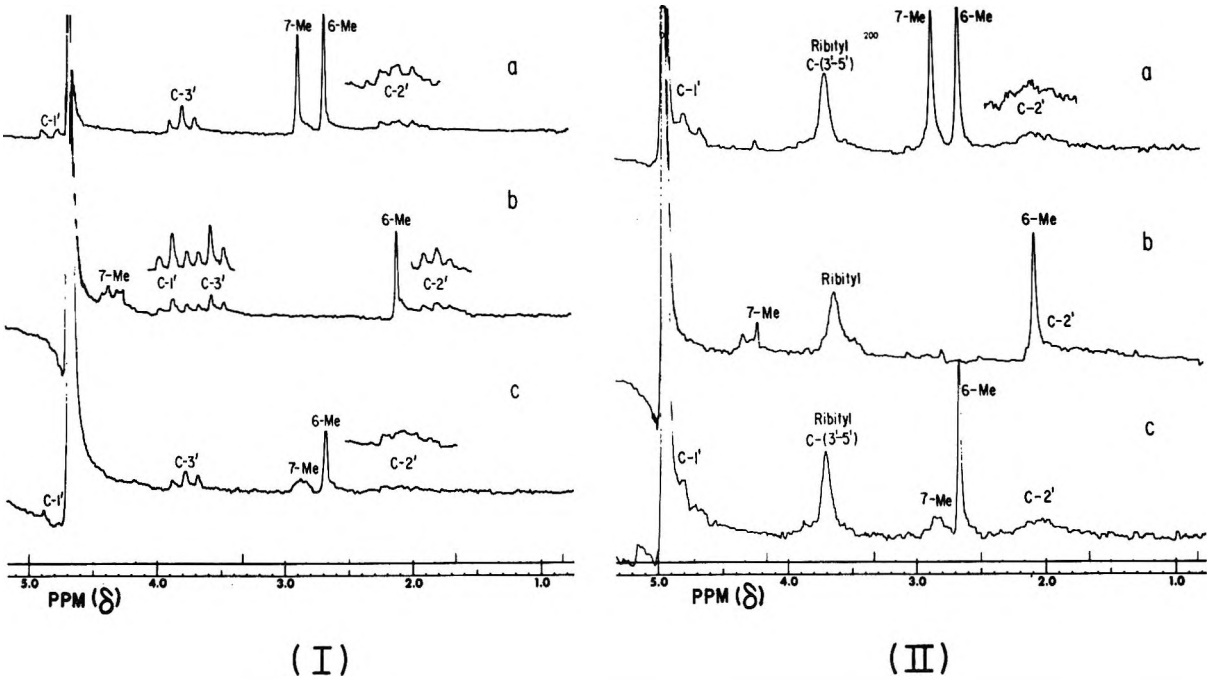


Figure 5.—Nmr spectra of 6,7-dimethyl-8-substituted lumazines lacking a 2′-hydroxyl group: I, 6,7-dimethyl-8-[1′-(3′-hydroxypropyl)]lumazine, and II, 6,7-dimethyl-8-[1′-(2′-deoxy-D-ribityl)]lumazine. All readings were taken in D_2O at 7°. Compounds were dissolved in (a) D_2O, (b) adjusted to 0.1 *N* NaOD, and (c) neutralized with DCl as described under Methods.

group) and at −2.17 ppm (6-methyl group) are about equal (Figure 3B, I and II). Consequently, the peaks at −2.17 and −2.07 ppm are assigned to the 6-methyl groups of the intramolecular ether **5** and the 7-exo methylene forms **7**, respectively.

Analogs Lacking the 2′-Hydroxyl Group.—Compounds exhibit differences in their visible absorption spectra (Figure 2) as well as their nmr spectra, depending upon the presence (Figure 3B, I and II) or absence (Figure 3B, III and Figure 5b) of a 2′-hydroxyl group. The substances without the 2′-hydroxyl group do not absorb at −1.37 ppm, but exhibit peaks in the vicinity of −3.90 to −4.30 ppm (Figure 5b).

The absence of absorption at −1.37 ppm suggests that the intramolecular ether does not exist and consequently *can only be formed between the 2′-hydroxyl group and carbon 7 of the pteridine ring.* This point is best illustrated by the 3′-hydroxypropyl analog (Figure 5, I) and the 2′-deoxy-D-ribityl derivative (Figure 3, III, and Figure 5, II) which lack the 2′-hydroxyl group but have hydroxyl groups elsewhere on the 8 substituent. These hydroxyl groups (including OH at the 3′ position), however, appear incapable of interacting with the pteridine ring to form the intramolecular ether. Consequently, the long wavelength absorption is retained; lacking covalent bonds at carbon 7, the absorption at −1.37 ppm is not observed.

The lack of any high-field absorption (*e.g.*, Figure 3B, III) further suggests that a hydrated intermediate such as structure **2** is absent or present in very low concentration, since the 7-methyl group of the molecule would be expected to absorb in the vicinity of −1.20 to −1.50 ppm characteristic of other methyl carbinols. The absence of this absorption peak suggests that the 7-exo methylene intermediate may be formed by a direct elimination reaction (**4**, **6**, **7**) rather than following an initial hydration reaction (**1** to **2**).

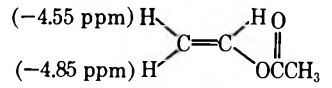
In H_2O the absorption by OH masks absorptions in the range of −3.80 to −4.60 ppm. This problem can be alleviated by the use of D_2O as the solvent. However, under such conditions it becomes necessary to slow the rate of hydrogen–deuterium exchange at the 7-methyl group. The spectra of the 3′-hydroxypropyl (Figure 5, I) and the 2′-deoxyribityl derivatives (Figure 5, II) were, therefore, recorded at 7° resulting in retention of sufficient protium at the 7-exo methylene group to show absorption in the vicinity of −3.90 and −4.30 ppm (Figure 5b). The 7-exo methylene group of 6,7,8-trimethyllumazine at 7° also exhibits absorption in this range,[2] shifted downfield from the −3.65-ppm value previously reported[25] at 37°.

Analogs lacking the 2′-hydroxyl group (Figure 5b) all exhibit two singlets in the vicinity of −3.90 to −4.30 ppm, attributed to the two nonequivalent hydrogens of the 7-exo methylene group of the molecule. The 7-exo methylene group should be coplanar with the pteridine ring resulting in a cis and trans orientation of the hydrogens of the group with respect to the pteridine ring. These hydrogens should therefore be nonequivalent and exhibit different chemical shifts, as was observed. The chemical shift of the 7-exo methylene group of the lumazine derivatives compares favorably with that of a number of methylene analogs [V (65), V (111), and V (596)] reported in the Varian Catalog[26] and 5-*H*-tetrahydrofavin cation.[27]

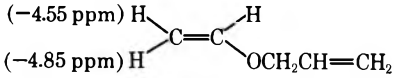
Confirmation that the two peaks in the vicinity of −3.90 to −4.30 ppm (Figure 5b) arise from the 7-methyl group is obtained upon neutra zation of the basic solution with 1.0 *N* DCl (Figure 5c). Residual absorption at −2.85 ppm due to the partially exchanged 7-methyl group (*cf.* Figure 5a) is observed.

The 6-methyl group, upon scale expansion (Figure 4e–g), appears as a single peak at −2.07 ppm. The

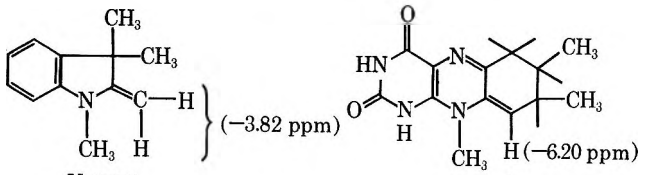
(27) (a) C. Heizmann, P. Hemmerich, R. Mengel, and W. Pfleiderer in "Chemistry and Biology of Pteridines," K. Iwai, M. Akino, M. Goto, and Y. Iwanami, Ed., International Academic Printing Co., Tokyo, Japan, 1970, p 105 (b) We wish to thank Dr. P. Hemmerich, Universität Konstanz (Konstanz, Germany), for communicating this information to us before publication.



V (65)



V (III)



V (596) **27a, b**

peak at −2.17 ppm assigned to the 6-methyl group of the intramolecular ether (Figure 4a–d) is absent.

Absorption at −3.90 to −4.30 ppm does not agree with the proposed α-methyl ketone **3** which would arise by ring opening,[2,4,5,10] since methyl ketones typically exhibit chemical shifts between −2.00 and −2.40 ppm but never downfield in the range of −4.00 ppm. Furthermore, the monooxime of 2,3-butanedione, a model compound to which the hypothetical α-methyl ketone **3** could be compared, exhibits an enhanced rate of hydrogen–deuterium exchange in alkaline solution, but absorption at −2.45 ppm disappears in less than 1 hr with only minor changes in its chemical shift (no change for the methyl α to the carbonyl and a shift to −1.82 ppm for the methyl β to the carbonyl). With the pteridine analogs, shifts from −2.85 ppm (**4**) to −3.90 to −4.30 ppm (**7**) were obtained.

Preliminary rate studies with the 3′-hydroxypropyl analog indicate that the first hydrogen of the 7-methyl group is removed instantly; the remaining two hydrogens exchange at a rapid but calculable rate. When 6,7-dimethyl-8-[1′-(3′-hydroxypropyl)]lumazine was dissolved in D_2O, made basic with NaOD, and immediately neutralized with DCl, only 1.7 of the 3 original hydrogens remained unexchanged. These data indicate that the first hydrogen is removed during the elimination reaction while the remaining hydrogens are exchanged with deuterium at a relatively slow rate, further suggesting that a hydrated intermediate **2** is not involved.

Occurrence of 7-Exo Methylene in 2′-Hydroxyl Group Bearing Compounds.—The position of equilibrium between the inner ether **5** and the 7-exo methylene **7** forms of compounds containing a 2′-hydroxyl group is difficult to establish by measurement at −3.90 to −4.30 ppm because of the technical restrictions imposed by OH absorption when H_2O is the solvent or by the hydrogen–deuterium exchange at the 7-methyl group which occurs when the determinations are made in D_2O. A more promising approach in determining the abundance of the 7-exo methylene form is by measuring the areas under the peaks of the absorption of the 6-methyl group at −2.07 and −2.17 ppm. In all of the compounds tested in 0.1 *N* NaOH, except one, less than 25% of the equilibrium mixture is due to the 7-exo methylene form (*e.g.*, Figure 4a–c). Although present in minor amounts, it should be emphasized that evidence for the existence of the 7-exo methylene group *has* been adduced from measurements at −2.10 to −2.20 ppm (Figure 4a–d) and at −3.90 to −4.30 ppm.[2] These results are, therefore, in accord with an equilibrium between compounds **7**, **4**, and **5**, indicated by the hydrogen–deuterium exchange which occurs with all of these forms of 2′-hydroxyl-substituted 6,7-dimethyllumazines.[2,25]

6,7-Dimethyl-8-[1′-(2′-hydroxyethyl)]lumazine is the only analog bearing a 2′-hydroxyl group which retains substantial visible absorption in alkaline solution (Figure 2). It seemed possible that with this compound the exo methylene form **7** is in higher concentration than the intramolecular ether form **5** in the equilibrium mixture. This appears to be confirmed by the nmr spectrum which shows in 0.1 *N* NaOH a relatively minor absorption at −1.37 ppm, *i.e.*, one-fourth that of the absorption between −2.20 and −2.10 ppm (6-methyl group).[2] Furthermore, scale expansion of the 6-methyl group (Figure 4d) exhibits two singlets; the singlet at −2.07 ppm (6-methyl group of the 7-exo methylene form **7**) is considerably larger than the absorption at −2.17 ppm (6-methyl group of the intramolecular ether form).

The shift in equilibrium, favoring the 7-exo methylene form and visible absorption, probably arises since the 2′-hydroxyl group of 6,7-dimethyl-8-[1′-(2′-hydroxyethyl)]lumazine is not confined to a rigid conformation as are the 2′-hydroxy groups of the higher homologs. Consequently, removal of a proton from the 7-methyl group by hydroxide ion can result in sufficient electrostatic repulsion to force the relatively unhindered 2′-hydroxyl group of the 2′-hydroxyethyl analog away from the 7-carbon of the pteridine ring as the electron pair is accommodated establishing a π bond with carbon 7. Steric and electrostatic effects of the neighboring hydroxyl groups of the higher homologs resist this electrostatic repulsion and thus remain primarily in the intramolecular ether form.

Registry No.—2-Deoxy-D-ribose oxime, 31735-35-0; D-threitylamine, salicylidine derivative, 31735-36-1; D-erythritylamine, salicylidine derivative, 31735-37-2; L-erythritylamine, salicylidine derivative, 31735-38-3; 2-deoxy-D-ribitylamine, salicylidine derivative, 31735-39-4; D-ribitylamine, salicylidine derivative, 31735-40-7.

Acknowledgment.—We wish to thank Dr. F. W. Holly of Merck and Co. for a gift of methyl 2,3-dehydro-D-ribofuranoside. We thank Dr. Peter Hemmerich for extensive correspondence and exchange of information dealing with nmr spectra of various lumazine derivatives.

Synthesis of β-Sitosteryl Acetate [(24*R*)-24-Ethyl-3β-acetoxycholest-5-ene] and Its 24*S* Epimer[1]

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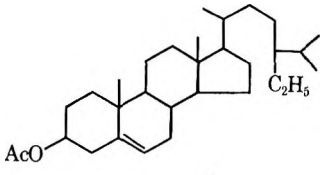
Received April 28, 1971

A semitotal synthesis of β-sitosteryl acetate and its 24*S* epimer (clionasterol) has been carried out, starting from the optically active 3-ethyl-4-methylpentylmagnesium bromides and pregnenolone acetate.

In a previous communication[2a] we have described the synthesis of campesteryl acetate and its 24*S* epimer. We then reported that the two epimers are differently utilized by the larvae of *Dermestes maculatus*. In order to clarify further the correlation between the stereochemical arrangement of C-24 alkyl groups and the biological activity of the sterols, we have synthesized β-sitosteryl acetate **1** and its 24*S* epimer (clionasteryl acetate) **2**.[2b]

β-Sitosteryl acetate **1** was synthesized as follows. Dextrarotatory 4-ethyl-5-methylhexanoic acid (**3**) was converted to 3-ethyl-4-methylpentyl bromide (**4**) by the Hunsdieker reaction. Grignard reaction of pregnenolone acetate with 3-ethyl-4-methylpentylmagnesium bromide yielded (24*R*)-24-ethyl-3β-acetoxycholesta-5,20(22)-diene (**5**) which was selectively reduced to (24*R*)-24-ethyl-3β-acetoxycholest-5-ene (β-sitosteryl acetate, **1**). The parallel synthesis using the optical antipode of **3** yielded the 24*S* epimer **2** of **1**, clionasteryl acetate.



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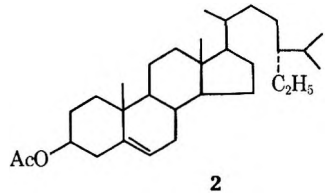

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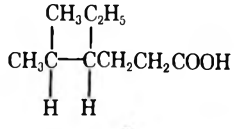

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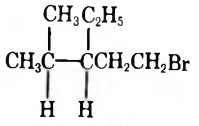

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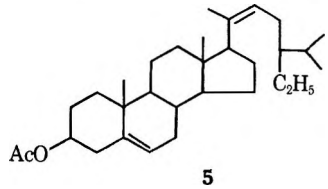

5

In agreement with our previous experience, only cinchonidine brought about the resolution of 4-ethyl-5-methylhexanoic acid into its optical isomers, whereas brucine, quinine, and 3-*p*-nitrophenyl-2-aminopropane-1,3-diol failed to do so.

Experimental Section[3]

Diethyl ethylmalonate was prepared according to Vogel.[4]

2-Ethyl-3-methylbutyric acid was prepared according to Ikan, *et al.*,[2a] starting from diethyl ethylmalonate, bp 115° (30 mm), yield 70%.

Anal. Calcd for $C_7H_{14}O_2$: C, 64.6; H, 10.9. Found: C, 64.6; H, 10.7.

Methyl 2-ethyl-3-methylbutyrate was prepared according to Ikan, *et al.*,[2a] bp 123–126°, yield 90%.

Anal. Calcd for $C_8H_{16}O_2$: C, 66.7; H, 11.1. Found: C, 66.4; H, 11.3.

2-Ethyl-3-methylbutanol.—To a slurry of 23 g of lithium aluminum hydride in 385 ml of dry ether, 100 g of the preceding ester in 240 ml of the same solvent was added with vigorous agitation. The mixture was refluxed for 6 hr, cooled (the excess of lithium aluminum hydride was destroyed with methanol), and acidified with dilute hydrochloric acid. The product was thoroughly extracted with ether (after the aqueous layer was saturated with sodium chloride) and dried, bp 145°, yield 68 g (77%).

Anal. Calcd for $C_7H_{16}O$: C, 72.4; H, 13.8. Found: C, 72.2; H, 13.9.

2-Ethyl-3-methylbutyl Bromide.—To a cooled solution (0°) of 2-ethyl-3-methylbutanol (35 g), 30 g of phosphorus tribromide was added dropwise. After 15 hr, ice was added and the organic layer separated. It was washed twice with 1-ml portions of concentrated sulfuric acid, twice with water, and with a dilute solution of sodium bicarbonate (10%). After drying over magnesium sulfate, the product was distilled, bp 65° (30 mm), yield 27.5 g (50%).

4-Ethyl-5-methylhexanoic Acid (3).—To a solution of 12 g of sodium in 250 ml of anhydrous ethanol, 79 g of diethyl malonate was added and the temperature was raised to 60°. Then 90 g of 2-ethyl-3-methylbutyl bromide was added dropwise during 45 min and the mixture refluxed with stirring for 25 hr. The precipitated sodium bromide was filtered off and the filtrate refluxed for 2 hr with 60 g of potassium hydroxide in 80 ml of ethyl alcohol, until neutral. Then 50 ml of water was added, the alcohol distilled off, and the residue acidified with concentrated hydrochloric acid and boiled for 10 hr. The product was extracted with methylene chloride, washed with a solution of sodium bicarbonate (10%) and water, and dried over anhydrous magnesium sulfate, bp 145° (25 mm), yield 45 g (58%).

Anal. Calcd for $C_9H_{18}O_2$: C, 68.3; H, 11.5. Found: C, 68.2; H, 11.6.

Resolution of 4-Ethyl-5-methylhexanoic Acid.—The acid and cinchonidine (1 mol each) were dissolved in acetone; the mixture was heated until the solution became clear and then allowed to crystallize at room temperature. The crystals of the salt were filtered on a Büchner funnel as soon as they formed. After five recrystallizations from acetone the salt was treated with dilute hydrochloric acid and the acid was extracted with methylene chloride and distilled under reduced pressure. The optical rotation of the product was $[\alpha]_D$ −8°.

(1) This work was supported in part by U. S. Department of Agriculture, Grant No. FG-Is-268.

(2) (a) R. Ikan, A. Markus, and E. D. Bergmann, *Steroids*, **16**, 517 (1970). (b) Preliminary tests have indicated that clionasterol is partially utilized by *Dermestes maculatus*.

(3) Melting points were determined on a Thomas-Hoover apparatus. Optical rotations were measured in chloroform. Nmr spectra were recorded for deuteriochloroform solutions using a Varian Hz-100 spectrometer. Infrared spectra were recorded on a Perkin-Elmer 137 spectrophotometer, using Nujol oil.

(4) A. I. Vogel, "Practical Organic Chemistry," Longmans, Green and Co., New York, N. Y., 1962, p 1002.

(−)-3-Ethyl-4-methylpentyl Bromide (4).—The levorotatory acid (4.5 g) was dissolved in 15 ml of carbon tetrachloride in a three-necked flask (protected from light with aluminum foil). Then 6.6 g of mercuric oxide was added followed, after a short heating period, by 4.8 g of bromine in 15 ml of carbon tetrachloride which was added dropwise. The solution was refluxed for 1 hr, the mercuric bromide filtered off, and the filtrate washed with a solution of sodium hydroxide (5%) and water. The product was fractionally distilled, bp 80° (20 mm), yield 2.1 g (40%), $[\alpha]_D$ −3°.

(24*S*)-24-Ethyl-3β-acetoxycholesta-5,20(22)-diene.—To the Grignard reagent prepared from 0.6 g of magnesium and 2.5 g of (−)-3-ethyl-4-methylpentyl bromide in 50 ml of ether, 1.8 g of 3β-acetoxypregn-5-en-20-one (pregnenolone acetate) in 50 ml of dry benzene was added, and the mixture was refluxed for 4 hr and allowed to stand overnight at room temperature. Hydrochloric acid (5%) was added and the product was extracted with benzene. Distillation of the benzene left an oily residue which was treated with 10 ml each of acetic anhydride and dry pyridine and left overnight at room temperature. Then 20 ml each of methanol and benzene was added, and the solution was concentrated *in vacuo*. This operation was repeated several times in order to remove the last traces of pyridine and acetic anhydride. The oily residue was chromatographed on a Florisil (60 g) column. The products were eluted with 100 ml each of solutions of benzene in hexane with the following concentrations, 5, 10, 20, 50% (v/v), followed by solutions of chloroform in benzene, 5 and 50% (v/v), and finally with chloroform. The product was recrystallized from methanol and melted at 135°, yield 0.5 g (30%), $[\alpha]_D$ −73.5°. The molecular ion in the mass spectrum was 394 (calcd, 394); ν_{max}^{Nujol} 1730 (CH_3COO^-), 975, 1640 cm^{-1} (C=C); nmr δ 5.2 ppm (>C=CH). Obviously, the tertiary alcohol formed in the Grignard reaction had undergone spontaneous dehydration.

(24*S*)-24-Ethyl-3β-acetoxycholest-5-ene (Clionasteryl Acetate) (2).—(24*S*)-24-Ethyl-3β-acetoxycholesta-5,20(22)-diene (30 mg) was dissolved in 10 ml of ethyl acetate and reduced catalytically in a microhydrogenator[5] in the presence of Pd/C (10%). The hydrogenation was stopped after saturation of the 20,22 double bond. The residue was recrystallized from methanol, yielding 28 mg of crystals melting at 139° (lit.[6] mp 143–144°), $[\alpha]_D$ −44.9° (lit.[6] $[\alpha]_D$ −45.3°). The molecular ion in the mass spectrum was 396 (calcd, 396).

Synthesis of (24*R*)-24-Ethyl-3β-acetoxycholesta-5,20(22)-diene (5). (+)-4-Ethyl-5-methylhexanoic Acid.—The mother liquors of the last two fractional crystallizations of cinchonidine (−)-4-ethyl-5-methylhexanoate were concentrated and the residue was treated with dilute hydrochloric acid. The acid was extracted with methylene chloride and distilled under reduced pressure, bp 145° (25 mm), yield 20%, $[\alpha]_D$ +8°.

(+)-3-Ethyl-4-methylpentyl bromide was prepared analogously to the (−) isomer, bp 80° (25 mm), yield 1.8 g (40%), $[\alpha]_D$ +3°.

(24*R*)-24-Ethyl-3-acetoxycholesta-5,20(22)-diene was prepared analogously to the 24*S*-ethyl isomer: mp 129°; yield 28%; $[\alpha]_D$ −84.3°; molecular ion in the mass spectrum 394 (calcd, 394); ν_{max}^{Nujol} 1730 cm^{-1} (CH_3COO^-); nmr δ 5.2 ppm.

(24*R*)-24-Ethyl-3β-acetoxycholest-5-ene (β-Sitosteryl Acetate) (1).—The catalytic hydrogenation was carried out analogously to the 24*S* epimer. The product melted at 121–122° after recrystallization from methanol: mp 124–125°; $[\alpha]_D$ −43° (lit.[7] mp 127°; $[\alpha]_D$ −41°); molecular ion 396 (calcd, 396); ν_{max}^{Nujol} 1730 cm^{-1} (CH_3COO^-).

Biological Tests.—The dietary components of the semisynthetic diet[8] were thoroughly extracted with ether, in order to remove traces of sterols. Sterol additions (0.1%) were made to the diet. Each sterol was tested on at least 20 larvae of *Dermestes maculatus* in 2–4 replications. The results of the tests are summarized in Table I.

TABLE I

Sterol	Av wt of larva (mg) after 25 days	% larvae pupating	Mortality of larvae
Sterol free (control)		None	Complete
Cholesteryl acetate	38	100	None
Campesteryl acetate[a]	33	95	1 in 20
β-Sitosteryl acetate[a]	2	None	Complete
Clionasteryl acetate[a]	3	None	Complete

[a] Synthetic; infrared and mass spectra of the synthetic sterols were identical with those of the natural sterols. No depression of melting points was observed on admixture of the synthetic and the natural compounds.

Registry No.—**1**, 915-05-9; **2**, 4651-54-1; (−)-**3**, 32444-27-2; (+)-**3**, 32444-28-3; (−)-**4**, 32444-29-4; (+)-**4**, 32444-30-7; (24*R*)-**5**, 32444-31-8; (24*S*)-**5**, 32444-36-3; 2-ethyl-3-methylbutyric acid, 32444-32-9; methyl 2-ethyl-3-methylbutyrate, 32444-33-0; 2-ethyl-3-methylbutanol, 32444-34-1; 2-ethyl-3-methylbutyl bromide, 32444-35-2.

Acknowledgment.—The authors wish to thank Mr. G. Grossman for the biological tests.

(5) N. Clauson-Kaas and F. Limborg, *Acta Chem. Scand.*, **1**, 884 (1949).
(6) W. Bergmann and E. M. Low, *J. Org. Chem.*, **12**, 67 (1947).
(7) E. S. Wallis, *ibid.*, **2**, 341 (1937).
(8) Z. H. Levinson, Y. Barelkovsky, and A. Bar-Ilan, *J. Stored Prod. Res.*, **3**, 345 (1967).

The Chemistry of Carpesterol, a Novel Sterol from *Solanum xanthocarpum*

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Received April 30, 1971

The structure of carpesterol (1) has recently been shown to be (22*R*)-22-hydroxy-6-oxo-4α-methyl-5α-stigmast-7-en-3β-yl benzoate. The present work describes some chemical transformations of the sterol as well as its degradation to 4α-methyl-5α-stigmast-8(14)-en-3β-ol (10) from which the 24*R* configuration of the stigmasterol ethyl group was confirmed. The possible implications of 1 to the biogenesis of steroidal alkaloids and sapogenins are presented. The ORD spectra of 1 and some of its derivatives are contrasted with the spectra of the ecdysterols.

Solanum xanthocarpum (Schrad. and Wendl.) has held a place of some importance in the Hindu *materia medica* primarily as an expectorant and antipyretic.[1,2] In 1936 Saiyed and Kanga[3] isolated the substance carpesterol along with a steroidal alkaloid glycoside and alkamine later identified as solasonine and solasodine,[4] respectively. Subsequent investigations of extracts from *S. xanthocarpum* showed the presence of diosgenin[5,6] and β-sitosterol.[6]

As part of our continuing interest in the chemistry and biogenetic relationship of the *Solanum* genus, we undertook the structural and chemical investigation of carpesterol.

Structure of Carpesterol.—In a recent communication[7] we reported the structure of carpesterol as determined by a combination of chemical, spectroscopic, and X-ray diffraction methods. For the application of the latter technique the nicely crystalline *p*-iodobenzenesulfonate derivative (pipsylate) of carpesterol was utilized. Figure 1 is a perspective drawing of carpesterol pipsylate as interpreted by ORTEP[8] showing all the nonhydrogen atoms in the unit cell as thermal ellipsoids and the extended conformation of the side chain and the benzoyl group as it exists in the crystalline state. By assuming that the configurations at C-10 and C-13 are identical with those of cholesterol, the absolute configurations of the side-chain asymmetric centers were determined by internal comparison to be 20*S*, 22*R*, and 24*R*.

Thus, carpesterol is (22*R*)-22-hydroxy-6-oxo-4α-methyl-5α-stigmast-7-en-3β-yl benzoate which can be considered an oxidized elaboration of the (24*R*)-24-ethyllophenol skeleton. As such, carpesterol logically fits into the phytosterol biogenetic scheme suggested by Goad[9] wherein citrostadienol (24-ethylidene lophenol) is placed as a precursor to 24-ethyllophenol. Work has been completed in this laboratory on the identification of sterol components of *S. xanthocarpum* other than carpesterol and will be reported separately.[10]

Bearing in mind that solasodine, the major steroidal alkaloid of *S. xanthocarpum*,[3] contains a spiroaminoketal grouping at C-22 and in a similar way the sapogenin, diosgenin, also found in the same plant,[5,6] has a spiroketal function at C-22, it was gratifying when the structure determination of carpesterol revealed a 22-hydroxyl group. According to biogenetic schemes presented by two authors,[11,12] an intermediate common to both steroidal alkaloids and sapogenins was postulated as a 16-hydroxycholesterol derivative having unsaturations at the side-chain positions, 22 and 25. Oxidation of the double bonds by plant metabolism could then lead to 16-dihydrokryptogenin, which in turn, when cyclized, would afford alkaloids or sapogenins. It is tempting to speculate that carpesterol arises in *S. xanthocarpum* as a result of a branching in the biogenetic pathway that leads to solasodine and diosgenin. If solasodine, diosgenin, and carpesterol are formed from the common intermediate indicated in Scheme I,[13] the sequence of events that produces carpesterol is characterized by incomplete 4-demethylation and by the utilization of the terminal double bond to promote alkylation rather than hydroxylation. Whether demethylation at C-4 is incomplete because of adverse steric influence by the 3β-benzoyloxy substituent is open to further speculation.

Relevant to the present discussion is the isolation of sarsasapogenin as a saponin[14] along with (22*S*)-22-hydroxycholesterol[15] from *Narthecium ossifragum*. Thus, there are now two reported instances of steroidal materials spiroketalized at C-22 that have been found in plants accompanied by 22-hydroxysterols.

Chemistry.—In order to characterize the 6-oxo-7-ene chromophore in the uv, it was necessary to remove the interfering benzoyl group. Simple hydrolysis with ethanolic HCl or NaOH was not effective. Although benzoic acid was isolated from the hydrolysates, the neutral product was a complex (tlc) mixture. Inspection of the ir carbonyl region of the crude neutral fraction suggested that the Δ^7 double bond had been, in part, isomerized out of conjugation with the 6-keto group. Reduction of carpesterol (1) with $LiAlH_4$ followed by regeneration of the 6-keto function with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), pro-

(1) K. T. Kirtikar and B. D. Basu, "Indian Medicinal Plants," Part II, The Indian Press, 1918, p 896.

(2) R. N. Chopra, S. L. Nayar, and I. C. Chopra, "Glossary of Indian Medicinal Plants," C. S. I. R., New Delhi, 1956, p 230.

(3) I. Z. Saiyed and D. D. Kanga, *Proc. Indian Acad. Sci.*, **4A**, 255 (1936).

(4) L. H. Briggs, *J. Amer. Chem. Soc.*, **59**, 1404, 2467 (1937).

(5) Y. Sato and H. G. Latham, *ibid.*, **75**, 6067 (1953).

(6) M. R. Heble, S. Narayanaswami, and M. S. Chadha, *Science*, **161**, 1145 (1968).

(7) Y.-H. Tsay, J. V. Silverton, J. A. Beisler, and Y. Sato, *J. Amer. Chem. Soc.*, **92**, 7005 (1970).

(8) C. K. Johnson, ORTEP (ORNL-3794), Oak Ridge National Laboratory, Oak Ridge, Tenn.

(9) L. J. Goad in "Terpenoids in Plants," J. B. Pridham, Ed., Academic Press, London, 1967, pp 182, 183.

(10) G. Kusano, Y. Sato, and J. A. Beisler, manuscript in preparation.

(11) K. Schreiber in "The Alkaloids," Vol. X, R. H. F. Manske, Ed., Academic Press, New York, N. Y., 1968, pp 122, 123.

(12) H. R. Schütte in "Biosynthese der Alkaloide," K. Mothes and H. R. Schütte, Ed., Deutscher Verlag der Wissenschaften, VEB, Berlin, 1969, p 628.

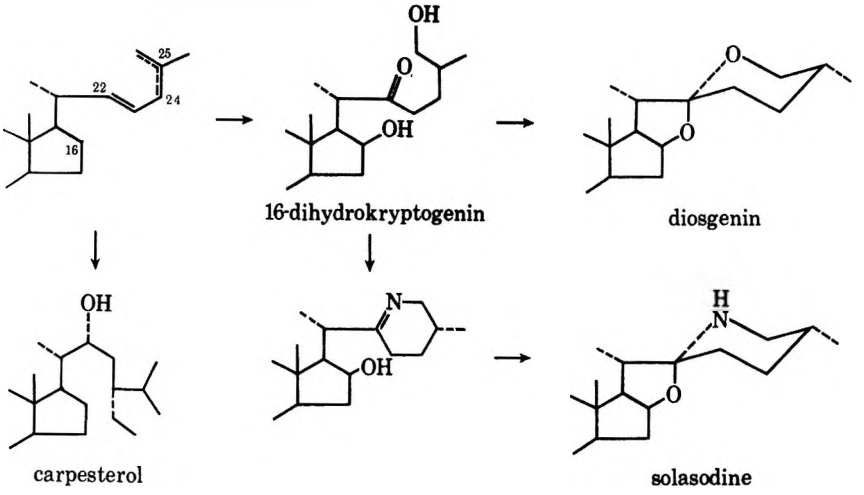
(13) Scheme I is an abbreviated and slightly modified form of the more comprehensive biogenetic schemes published elsewhere.[11,12]

(14) A. Stabursvik, *Acta Chem. Scand.*, **8**, 1304 (1954).

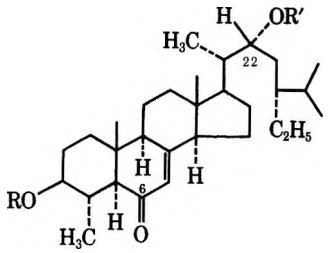
(15) A. Stabursvik, *ibid.*, **7**, 1220 (1953).

SCHEME I

BIOGENETIC RATIONALIZATION OF THE STEROIDAL PRODUCTS FROM *S. xanthocarpum*



vided a route to debenzoylcarpesterol which was isolated as the diacetate (2). Diacetate 2 gave a maxi-



1, R = COPh; R′ = H
2, R = R′ = $COCH_3$
3, R = COPh; 22-oxo
4, R = COPh; R′ = $SO_2C_6H_4CH_3$
5, R = COPh; 22-oxo; 6ξ-H, 6ξ-OH

mum in the uv at 245 mμ (ε 12,500) which agrees well with the calculated value (244 mμ) for a trisubstituted α,β-unsaturated ketone.[16]

Since 2 gives an ORD spectrum similar in appearance and amplitude to the curve obtained for carpesterol (1) (Figure 2), it is reasonable to assume that no stereochemical alterations occurred when converting 1 into 2. Again with reference to Figure 2, the enantiomeric environment of the 12-oxo-9(11)-ene chromophore of 12-oxolanost-9(11)-en-3β-yl acetate[17] with respect to the 6-oxo-7-ene chromophore of 1 is evident in the near mirror-image relationship of their ORD curves. Although the steroidal insect-metamorphosing hormones (ecdysterols), which also have 6-oxo-7-ene chromophores, give ORD curves that are similar in sign and appearance to 1 and 2, the amplitudes are significantly smaller. The difference can be attributed to the ecdysterol 5β configuration where 1 and 2 have a 5α hydrogen at the A–B ring junction.[18] The range of the absolute magnitudes of the amplitudes for the curves shown in Figure 2 (*i.e.*, 450–570) is higher by a factor of *ca.* 6 than the 68–110 range reported[19] for five ecdysterols. This observation could be used to determine the absolute configuration at C-5 in 6-oxo-7-ene steroids and perhaps at C-13 in the case of 12-oxo-9(11)-ene steroids.

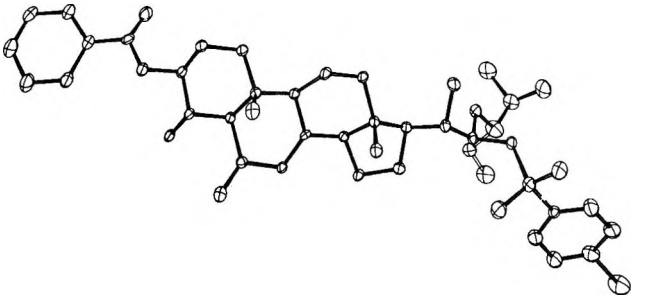


Figure 1.—An ORTEP projection from an input of the positional and anisotropic thermal parameters of carpesterol pipsylate.

There have been a number of examples recorded in the literature pointing to a diminished reactivity with respect to reduction of the 22-keto group in the side chain of cholesterol derivatives. For example, Mazur, *et al.*,[20] made use of this property in a sapogenin synthesis. We have found indications that C-22 in ketocarpesterol (3) and carpesterol tosylate (4) has a similar reduced reactivity with nucleophilic reagents. When 3, formed by chromic acid oxidation of carpesterol, was reduced with sodium borohydride a single product was isolated in good yield. Structure 5, which indicates a preferential reduction of the 6-keto group, was assigned to the reduction product on the basis of its ir spectrum and combustion analysis. This structure assignment was supported by the regeneration of 3 by allylic oxidation with DDQ. When tosylate 4 is refluxed with $LiAlH_4$ in THF, displacement of the tosylate group does not occur, but instead, the energetically favored reaction, the elimination of the elements of toluenesulfonic acid to form a double bond (Scheme II), occurs.

The action of $LiAlH_4$ on tosylate 4 not only leads to 22 unsaturation, but also reduces the 6-keto function and reductively removes the benzoyl group to provide intermediate 6. This intermediate was particularly useful in the degradation of carpesterol. Successive

(16) A. I. Scott, "Interpretation of the Ultraviolet Spectra of Natural Products," Pergamon Press, London, 1961, p 58.

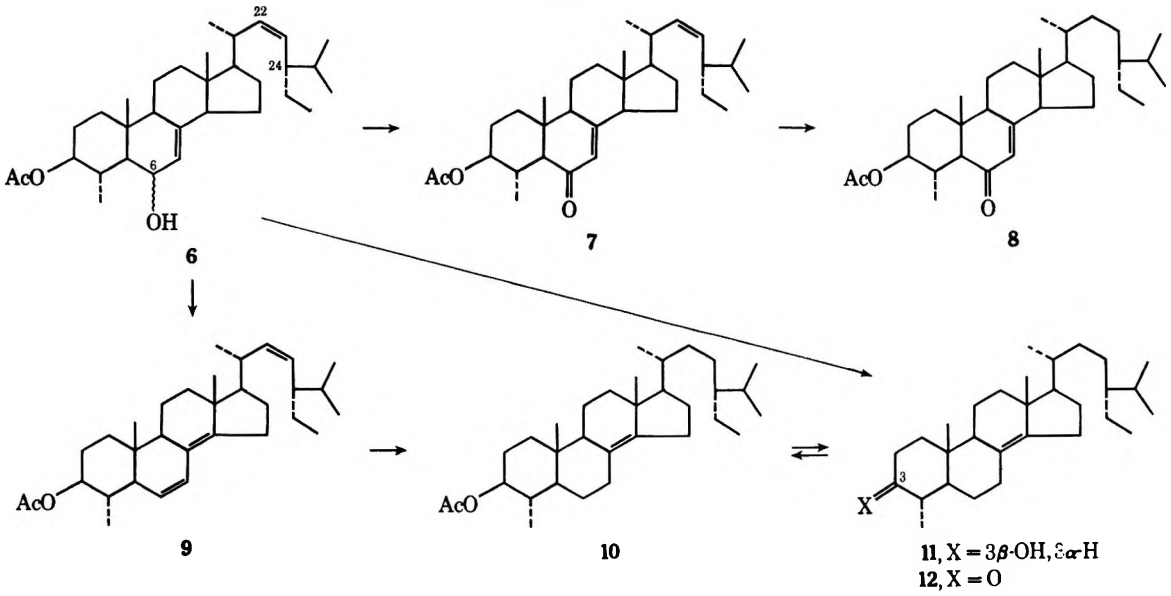
(17) We express our gratitude to Professor W. Lawrie, University of Strathclyde, Glasgow, for providing a sample of this compound.

(18) Carpesterol (1) does not have insect-metamorphosing hormonal activity. The authors thank M. J. Thompson, U. S. Department of Agriculture, Beltsville, Md., for providing this assay.

(19) H. Hikino, K. Nomoto, and T. Takemoto, *Tetrahedron*, **26**, 887 (1970).

(20) Y. Mazur, N. Danieli, and F. Sondheimer, *J. Amer. Chem. Soc.*, **82**, 5889 (1960).

SCHEME II



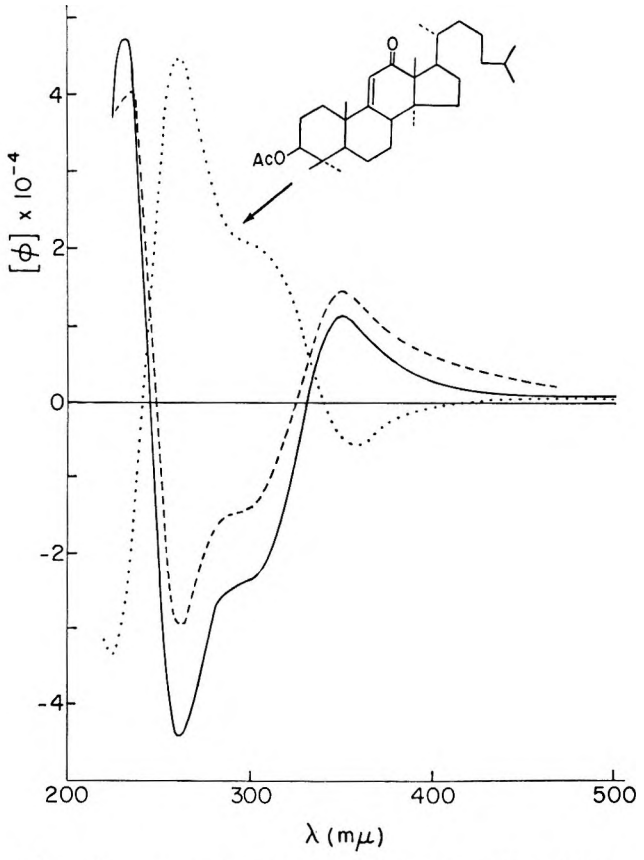


Figure 2.—ORD spectra of carpesterol (**1**, $a = +570$, solid line), debenzoylcarpesterol diacetate (**2**, $a = +450$, broken line), and 12-oxolanost-9(11)-en-3β-yl acetate ($a = -515$, dotted line).

treatments with DDQ and acetic anhydride converted **6** to debenzoylanhydrocarpesterol acetate (**7**). That the newly formed double bond in **6** and **7** occupies the 22 position was shown by the absence of a signal in the nmr attributable to a methyl group substituted on a sp^2-hybridized carbon atom (excepting the acyl methyl) and by the appearance of three protons in the olefinic region of the spectrum. Catalytic uptake of 1 mol equiv of hydrogen by **7** gave debenzoyldeoxycarpesterol acetate (**8**), the ORD spectrum ($a = 499$) of which was similar to those of **1** and **2**.

By applying a different sequence of reactions to intermediate **6**, known compounds were obtained from which it was possible to compare the absolute configuration of the C-24 ethyl groups of carpesterol and stigmasterol. Accordingly, acetylation of **6** followed by mild acid treatment produced a 6,8(14),22-triene acetate (**9**) which showed a maximum in the uv at 250 mμ (ε 19,400) comparable to ergosta-6,8(14),22-trien-3β-yl, acetate (ϵ_{252}^{max} 24,000).[21a] Both the latter compound[21b] and **9** exhibited negative Cotton effects in their ORD curves.[22] Hydrogenation of **9** results in uptake of 2 mol equiv of hydrogen to afford 4α-methyl-5α-stigmast-8(14)-en-3β-yl acetate (**10**, mp 131–132°, $[\alpha]D$ +39°). Direct hydrogenation of intermediate **6** leads to hydrogenolysis of the allylic alcohol, saturation of the side-chain double bond, and isomerization of the nuclear double bond to the 8(14) position to give alcohol **11** (mp 147–148°, $[\alpha]D$ +18°). Chromic acid oxidation of **11** provided the 3-keto derivative (**12**), which gave a positive Zimmerman reaction[24] and the anticipated positive Cotton effect in the ORD indicative of 4α-methyl-A/B trans steroids.[25] The ORD spectrum of **12**, which requires the cholesterol absolute configuration at C-10, supports the validity of our earlier assumption in choosing the enantiomorph of carpesterol pipsylate from the two possibilities offered by the X-ray data. Hydride reduction of **12** returned alcohol **11**, and acetylation of the latter gave an acetate that was identical (mixture melting point, ir) with acetate **10** prepared by the alternate route described above.

For the purpose of a structure determination, Mazur,

(21) (a) G. D. Laubach, E. C. Schreiber, E. J. Angello, and K. J. Brunings, *J. Amer. Chem. Soc.*, **78**, 4743 (1956); (b) E. Charney, H. Ziffer, and U. Weiss, *Tetrahedron*, **21**, 3121 (1965).

(22) The ergostatriene and **9** do not follow the transoid diene rule[22a] for prediction of the Cotton effect sign, perhaps due to the small skew angles required by their structures (see ref 21b, p 3124). This being true, the two additional methyl groups at C-4 and C-28 of **9** are not sufficient to change the skew sense of the diene with a concomitant change in the sign of the Cotton effect. The CD spectrum of the ergostatriene, however, conforms to theoretical predictions.[23]

(23) See ref 20 in A. W. Burgstahler and R. C. Barkhurst, *J. Amer. Chem. Soc.*, **92**, 7601 (1970).

(24) D. H. R. Barton and P. deMayo, *J. Chem. Soc.*, 887 (1954), and references cited therein.

(25) P. Crabbé, "Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry," Holden-Day, San Francisco, Calif., 1965, p 46.

et al.,[26] hydrogenated citrostadienol and its acetyl derivative to give isocitrostenol (mp 152–153°, $[\alpha]_D$ +23°) and isocitrostenol acetate (mp 129–130°, $[\alpha]_D$ +41°), respectively. Complete saturation of isocitrostenol occurred by hydrogenation under acidic conditions to yield 4α-methyl-5α-stigmastan-3β-ol. The identity of the last mentioned derivative was established by synthesis from stigmasterol. Thus, the adequate agreement of the melting points and rotations of **10** and **11** with isocitrostenol acetate and isocitrostenol, respectively, indicates an identity between the corresponding pairs, and it follows that the absolute configuration of the C-24 ethyl group is the same in stigmasterol, isocitrostenol,[27] and carpesterol.

The absolute configuration of the side-chain ethyl group of stigmasterol was determined by Tsuda and coworkers[28] by ozonolysis of the 22 double bond and conversion of the resulting fragment into a compound of known absolute configuration. The chemical degradation of **1** in conjunction with our X-ray study of carpesterol pipsylate confirms the 24*R* configurational assignment for stigmasterol ethyl group.

Experimental Section

Melting points were determined on a Kofler micro hot stage and were not corrected. Ir and uv spectra were recorded with a Perkin-Elmer Model 421 and a Cary Model 15 spectrophotometer, respectively. Rotations were measured in a 1-dm microcell in $CHCl_3$ solutions with a Perkin-Elmer Model 141 polarimeter. ORD curves were determined with a Cary Model 60 spectropolarimeter. Nmr spectra were measured in $CDCl_3$ solutions with a Varian Model A-60 spectrometer using TMS as an internal standard. The Hitachi Perkin-Elmer RMU-6 double-focusing mass spectrometer was used at 80 eV to record mass spectra.

Isolation of Carpesterol (1).—The dried and ground fruit from *S. xanthocarpum*[29] (7.7 kg) was extracted with 7 l. of *n*-hexane in a Soxhlet apparatus for 24 hr. The extract was concentrated to 1.5 l. by distillation of the solvent, allowed to stand at room temperature for 3 days, and then filtered. After washing thoroughly with fresh portions of hexane, 3.87 g of a tan powder was obtained. The powder was taken up in benzene–pentane and chromatographed on 110 g of Woelm alumina (neutral, activity II). After washing oils from the column with 500 ml of benzene–pentane mixtures, colorless crystals were eluted with benzene and benzene–Et_2O. Recrystallization from acetone gave 3.37 g (0.044% based on dried plant material) of **1** as glistening plates, mp 248–251°. The pure sterol was obtained from acetone–EtOH: mp 251° (lit.[3] mp 248°); $[\alpha]^{27}_D$ +67° (c 0.716); ORD (c 0.014, MeOH) $[\phi]_{600}$ +400°, $[\phi]_{350}$ +11,500°, $[\phi]_{295}$ −24,500° (sh), $[\phi]_{261}$ −44,500°, $[\phi]_{230}$ +47,600°; uv max (EtOH) 233 mμ (ε 19,400); ir ($CHCl_3$) 3590 (OH), 1710 (C=O, benzoate), 1677 (enone), 1632, 1607, 1587 cm^{-1}; nmr δ 8.2–7.3 (m, 5 H, aromatic protons), 5.71 (s, 1 H, C-7 proton), 4.71 (broad, 1 H, C-3 proton), and 3.76 (very broad doublet, 1 H, C-22 proton); mass spectrum *m/e* (rel intensity) 562 (9, M^+), 544 (16, M − H_2O), 529 (10, M − H_2O − Me), 501 (10), 440 (65, M − PhCOOH), 422 (22), 403 (19), 312 (100), 297 (18), 257 (69), 109 (45) 105 (88).

Anal. Calcd for $C_{37}H_{54}O_4$: C, 78.96. H, 9.67. Found: C, 78.70; H, 9.68.

Stirring **1** at room temperature for 24 hr in pyridine solution with excess *p*-iodobenzenesulfonyl chloride gave carpesterol pipsylate in quantitative yield as plates, mp 126–127°. Slow evaporation of a MeOH–CH_2Cl_2 solution provided crystals suitable for X-ray diffraction analysis.

Anal. Calcd for $C_{43}H_{57}O_6IS$: C, 62.31; H, 6.94; I, 15.32. Found: C, 62.05; H, 6.70; I, 15.36.

Debenzoylcarpesterol Diacetate (2).—Carpesterol (**1**) was reduced with $LiAlH_4$ in refluxing (3 hr) THF to give a quantitative yield of colorless needles after recrystallization from benzene.

A solution of 190 mg of the reduction product in 4 ml of dioxane treated with a solution of 200 mg of DDQ in 4 ml of dioxane and allowed to stand at room temperature for 44 hr. The reaction solution was poured into dilute NaOH solution and ether extracted, and the extracts were shaken twice with dilute NaOH and washed with water. Removal of the solvent gave a crystalline residue which was acetylated directly in the usual way with acetic anhydride–pyridine. A cyclohexane solution of the crude acetylated product was chromatographed on 13 g of Woelm (neutral, activity II) alumina. Elution with pentane–PhH mixtures afforded 131 mg of crystalline **2**: mp 205–206°; ORD (c 0.013, MeOH) $[\phi]_{600}$ +366°, $[\phi]_{348}$ +15,000°, $[\phi]_{295}$ −14,600°, $[\phi]_{263}$ −30,000°, $[\phi]_{231}$ +40,000; uv max (EtOH) 245 mμ (ε 12,500); ir (CS_2) 2875, 1768, 1686, 1634, 1245, 1142 cm^{-1}; mass spectrum *m/e* (rel intensity) 542 (4, M^+ requires 542.3971, found 542.3994), 482 (100, M − HOAc), 467 (12), 372 (22), 341 (23), 317 (23), 257 (57).

Anal. Calcd for $C_{34}H_{54}O_5$: C, 75.23; H, 10.03. Found: C, 75.24; H, 9.85.

Ketocarpesterol (3).—A modified Kiliani reagent[30] was prepared such that the concentration of the chromic acid provided 4 mequiv/ml. A microburet was used to drop 0.58 ml of the oxidant into a solution of 500 mg of **1** in 60 ml of acetone[31] stirred at room temperature. Stirring was continued for 15 min after the addition, then excess oxidant was destroyed with a few drops of *i*-PrOH and water was added dropwise until green droplets separated from solution. The solution was decanted, the decantate was evaporated, and the residue in ether solution was washed with 2% $NaHCO_3$ and water. The ether solution yielded 464 mg of crystalline **3**, which melted at 228–229° after recrystallization from acetone–MeOH: $[\alpha]^{20}_D$ +47° (c 0.9); ORD (c 0.013, MeOH) $[\phi]_{600}$ +200°, $[\phi]_{350}$ + 13,800°, $[\phi]_{300}$ −19,700° (sh), $[\phi]_{265}$ −38,100°, $[\phi]_{235}$ +50,300°; ir ($CHCl_3$) 2879, 1710, 1674, 1631, 1605, 1585 cm^{-1}; nmr δ 8.2–7.3 (m, 5 H, aromatic protons), 5.71 (s, 1 H, C-7 proton), and 4.75 (broad, 1 H, C-3 proton); mass spectrum *m/e* (rel intensity) 560 (28, M^+ requires 560.3865, found 560.3840), 545 (5), 518 (10), 477 (21), 438 (91), 354 (100).

Anal. Calcd for $C_{37}H_{52}O_4$: C, 79.24; H, 9.35. Found: C, 79.40; H, 9.09.

Carpesterol Tosylate (4).—A solution of 2.79 g of **1** in 20 ml of dry pyridine was combined with 2.92 g of *p*-toluenesulfonyl chloride and stirred at room temperature for 70 hr. The product was ether extracted from dilute HCl solution. While concentrating the dried ether extracts on a steam bath, *n*-hexane was slowly added until a saturated solution was obtained. On cooling, a quantitative yield of the tosylate was collected as colorless needles: mp 126–127°; ir (CS_2) 1715, 1682, 1627, 1365, 1267, 1173 cm^{-1}.

Anal. Calcd for $C_{44}H_{60}O_6S$: C, 73.70; H, 8.44; S, 4.47. Found: C, 74.00; H, 8.38; S, 4.31.

Borohydride Reduction of Ketocarpesterol (3).—Ketocarpesterol (74 mg), dissolved in 20 ml of THF–EtOH (1:1), was treated with 155 mg of $NaBH_4$ and stirred for 30 hr at room temperature. Concentration under vacuum gave a residue, 2% $NaHCO_3$ solution was added, and the solution was extracted with CH_2Cl_2. The evaporated extracts produced a gum that crystallized on standing. Recrystallization (acetone–water) gave 66 mg of **5**: mp 188–191°; ir ($CHCl_3$) 3620, 2960, 1711, 1607, 1120, 1072, 1027, 966 cm^{-1}.

Anal. Calcd for $C_{37}H_{54}O_4$: C, 78.96; H, 9.67. Found: C, 78.82; H, 9.51.

Using methanol as the reaction solvent gave the same product.

Ketocarpesterol (3) from 5.—To a solution of 66 mg of **5** in 4 ml of dioxane was added a solution of 90 mg of DDQ in 4 ml of dioxane, and the resulting clear yellow solution was stirred at

(26) Y. Mazur, A. Weizmann, and F. Sondheimer, *J. Amer. Chem. Soc.*, **80**, 6293 (1958).

(27) In the synthesis of 4α-methyl-5α-stigmastan-3β-ol, asymmetric centers were generated at the 4 and 5 positions in the reduction of 4-methylstigmast-4-en-3-one with H_2/Pd or Li/NH_3.[26] Not only does the present study confirm the 4α-methyl-5α-hydrogen assignment for the reduction product, but also confirms the correct stereochemical assignments at C-4 and C-5 of citrostadienol itself.

(28) K. Tsuda, Y. Kishida, and R. Hayatsu, *J. Amer. Chem. Soc.*, **82**, 3396 (1960).

(29) We are indebted to Dr. Quentin Jones, New Crops Research Branch, U. S. Department of Agriculture, Beltsville, Md., for making a generous supply of plant material available to us.

(30) H. Kiliani, *Chem. Ber.*, **46**, 676 (1913).

(31) R. G. Curtis, I. Heilbron, E. R. H. Jones, and G. F. Woods, *J. Chem. Soc.*, 457 (1953).

room temperature for 3 days. Work-up as for **2** gave a yellow solid which yielded 40 mg of white needles by crystallization from acetone–MeOH. The product (mp 221–225°) was identical with **3** (mixture melting point, ir, mass spectrum).

$LiAlH_4$ Reduction of Carpesterol Tosylate (4).—To a stirring mixture of 6.4 g of $LiAlH_4$ and 225 ml of dry THF was added dropwise a solution of 6.65 g of **4** in 75 ml of THF. The mixture was stirred and refluxed for 5 hr, cooled, and hydrolyzed with water. The reaction solution was poured into saturated Rochelle salt solution and ether extracted. Evaporation of the extracts and recrystallization of the residue from EtOAc gave 4.04 g of **6** as a crystalline solid which melted over a broad range and which showed no carbonyl absorption in the infrared. Repeated recrystallization (EtOAc) gave small prisms, mp 197–209°.

Anal. Calcd for $C_{30}H_{50}O_2$: C, 81.39; H, 11.38. Found: C, 81.09; H, 11.26.

Debenzoylanhydrocarpesterol Acetate (7).—Diol **6** (914 mg) was oxidized with 1.0 g of DDQ, and the crude product was acetylated as described for the preparation of **2**. From the crude acetylation product 536 mg of **7** was obtained by crystallization from MeOH: mp 200–201°; uv max (EtOH) 246 mμ (ε 13,000); ir (CS_2) 1735, 1682, 1630 cm^{-1}; nmr δ 5.76 (br s, 1 H, C-7 proton), 5.21 (m, 2 H, CH=CH), 4.5 (very broad, 1 H, C-3 proton), and 2.08 (s, 3 H, COMe); mass spectrum *m/e* (rel intensity) 482 (58, M^+ requires 482.3760, found 482.3769), 439 (36), 422 (41), 379 (32), 370 (20), 341 (100).

Anal. Calcd for $C_{32}H_{50}O_3$: C, 79.62; H, 10.44. Found: C, 79.32; H, 10.57.

Debenzoyldeoxycarpesterol Acetate (8).—At room temperature and pressure, 225 mg of **7** was hydrogenated in EtOAc solution (10 ml) to which 123 mg of 10% palladium/charcoal catalyst had been added. Hydrogen uptake was complete after 30 min. After filtration and evaporation of the reaction solution, 167 mg of **8** was obtained by recrystallization from MeOH: mp 188–189°; $[\alpha]^{23}D$ +26° (*c* 1.01); ORD (*c* 0.014 MeOH) $[\phi]_{348}$ +9700°, $[\phi]_{263}$ −40,200°; uv max (EtOH) 246 mμ (ε 12,500); ir (CS_2) 1743, 1690, 1636 cm^{-1}; mass spectrum *m/e* (rel intensity) 484 (12, M^+), 424 (100), 409 (37), 356 (67), 343 (14), 283 (22), 257 (37).

Anal. Calcd for $C_{32}H_{52}O_3$: C, 79.28; H, 10.81. Found: C, 79.13; H, 10.87.

4α-Methyl-5α-stigmast-6,8(14),22-trien-3β-yl Acetate (9).—Diol **6** (275 mg), obtained from the reduction of carpesterol tosylate, in 10 ml of dry pyridine was combined with 5 ml of acetic anhydride, stirred at room temperature for 15 hr, and then heated to 70–75° for 4 hr. After hydrolyzing the reaction solution with ice chips the product was isolated in the usual way to give a noncrystallizable gum which was homogeneous by tlc (PhH–EtOAc).

Dissolving the gum in 4 ml of glacial HOAc containing 0.1 ml of concentrated HCl caused crystals to separate slowly from solution (150 mg, mp 132–144°) (recrystallization from MeOH–CH_2Cl_2 raised the melting point to 154–155°): ORD (*c* 0.015, MeOH) $[\phi]_{400}$ −990°, $[\phi]_{300}$ −3800°, $[\phi]_{264}$ −17,700°, $[\phi]_{250}$ −4600°; uv max (EtOH) 250 mμ (ε 19,400); ir (CS_2) 3045, 2868, 1745, 1245, 1024, 973, 800, 689 cm^{-1}; nmr δ 5.39–5.06 (m, 4 H, olefinic protons), 4.38 (broad, 1 H, C-3 proton); mass spectrum *m/e* (rel intensity) 466 (56, M^+), 451 (31), 391 (19), 353 (13), 326 (100), 311 (34).

Anal. Calcd for $C_{32}H_{50}O_2$: C, 82.34; H, 10.80. Found: C, 82.45; H, 10.68.

4α-Methyl-5α-stigmast-8(14)-en-3β-yl Acetate (10) from 9.—Reduction of 38 mg of triene **9** in 4 ml of EtOAc with hydrogen at room temperature and pressure (47 mg of 10% palladium/charcoal catalyst) gave a quantitative yield of **10**: mp 131–132° (from MeOH–CH_2Cl_2); $[\alpha]^{24}D$ +39° (*c* 1.01); ir (CS_2) 2870, 1735, 1377, 1370, 1241, 1022 cm^{-1}; mass spectrum *m/e* (rel intensity) 470 (100, M^+), 455 (12), 410 (6), 395 (8), 329 (6), 287 (4), 269 (15), 243 (13), 227 (15), 147 (18), 135 (10), 133 (11); no olefinic protons appeared in the nmr.

Anal. Calcd for $C_{32}H_{54}O_2$: C, 81.64; H, 11.56. Found: C, 81.85; H, 11.51.

4α-Methyl-5α-stigmast-8(14)-en-3β-ol (11) from 6.—A solution of 510 mg of diol **6** in 15 ml of EtOAc was mixed with 285 mg of 10% palladium/charcoal catalyst and hydrogenated at room temperature and pressure for 4.5 hr. The catalyst was removed by filtration and thoroughly extracted (Soxhlet) with EtOAc, and the filtrate and extracts were combined and evaporated. Recrystallization of the product from MeOH–CH_2Cl_2 gave 379 mg of plates: mp 147–148°; $[\alpha]^{22}D$ +18° (*c* 1.02); ir (CS_2) 3620, 2870, 1378, 1368, 1212, 959 cm^{-1}; mass spectrum *m/e* (rel intensity) 428 (100, M^+ requires 428.4018, found 428.4017), 413 (25), 287 (20), 243 (17), 227 (19).

Anal. Calcd for $C_{30}H_{52}O$: C, 84.04; H, 12.23. Found: C, 84.15; H, 12.09.

Acetylation of **11** with pyridine/acetic anhydride gave acetate **10** (mp 131–132°), which was identical (mixture melting point, ir) with the hydrogenation product from triene **9**.

4α-Methyl-5α-stigmast-8(14)-en-3-one (12).—Alcohol **11** (257 mg), dissolved in 15 ml of acetone, was oxidized with 0.55 ml of the 4 *N* chromic acid reagent which was added dropwise to the stirred reaction solution. The product was isolated as described for ketocarpesterol (**3**). Accordingly, the extracts yielded 248 mg of a gum that spontaneously crystallized. Several recrystallizations from MeOH–CH_2Cl_2 gave pure ketone **12**: mp 110–112°; $[\alpha]^{22}D$ +18° (*c* 1.03); ORD (*c* 0.077, dioxane) $[\phi]_{400}$ +180°, $[\phi]_{312}$ +2400°, $[\phi]_{305}$ +2240° (sh), $[\phi]_{260}$ −8640°; ir (CS_2) 1709, 1374, 1365, 1174, 957 cm^{-1}; mass spectrum *m/e* (rel intensity) 426 (100), 412 (14), 411 (38), 285 (37), 272 (12), 259 (22), 258 (25), 243 (46).

Anal. Calcd for $C_{30}H_{50}O$: C, 84.44; H, 11.81. Found: C, 84.50; H, 11.59.

Addition of excess $LiAlH_4$ to an ethereal solution of ketone **12** (30 mg) gave, on work-up, 28 mg of alcohol **11**. Colorless plates (mp 143–147°) were obtained from MeOH–CH_2Cl_2 and a mixture melting point with **11** prepared from **6** showed no depression. The acetate (**10**) derivative (Ac_2O/py) had a melting point of 127–131° after one recrystallization from MeOH–CH_2Cl_2.

Registry No.—**1**, 31077-78-8; **1** pipsylate, 31077-79-9; **2**, 31893-26-2; **3**, 31893-27-3; **4**, 31893-28-4; **5**, 31893-29-5; **6**, 31893-30-8; **7**, 31893-31-9; **8**, 31893-32-0; **9**, 31893-33-1; **10**, 31893-34-2; **11**, 31893-35-3; **12**, 31893-36-4.

Acknowledgment.—We express our gratitude to Mrs. E. G. Peake (ir), Mrs. A. H. Wright (nmr), Mr. W. R. Landis (mass spectrum), Dr. W. C. Alford (elemental analyses), and Mr. D. L. Rogerson (large-scale extraction), all of this institute, for their assistance in this work.

Synthesis of Chlorobiumquinone[1]

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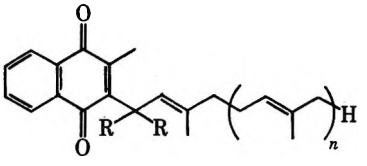
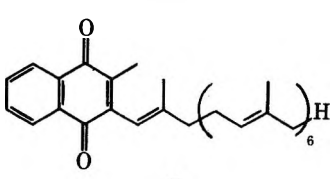
Received April 26, 1971

The synthesis of chlorobiumquinone, *all-trans*-1′-oxomenaquinone-7, is reported. A key intermediate in this synthesis is the naphthalenic fragment, 2-lithio-3-methyl-1,4-dimethoxynaphthalene, which when condensed with an α,β-unsaturated aldehyde side-chain component yields the dimethyl ether of 1′-oxymenaquinol. This allylic alcohol can either be oxidatively demethylated with acidic argentic oxide (AgO), leading to a 1′-oxymenaquinone, or oxidized first at the 1′ position with manganese dioxide and then demethylated to give a 1′-oxomenaquinone. In order to construct the all-trans C_{35} α,β-unsaturated aldehyde required for chlorobiumquinone synthesis, *all-trans*-farnesylfarnesylacetone (C_{33}) was assembled from geranylacetone (C_{13}) and the masked-functional ylide of triphenyl (4-methyl-8,8-ethylenedioxy-4-*trans*-nonenyl)phosphonium iodide as the C_{10} repeating unit. The first condensation gave geranylgeranylacetone (C_{23}) after hydrolysis of the ethylene ketal, and repetition of reaction with the masked-functional C_{10} ylide and hydrolysis gave farnesylfarnesylacetone (C_{33}). Δ^9-Cis,trans separation was effected by thiourea inclusion after each condensation. The other double bonds in the C_{33} unit are trans by virtue of their origin in geraniol. The masked-functional Δ^9-trans C_{10} phosphonium salt was prepared most efficiently by removing three carbons from the ethylene ketal of geranylacetone *via* terminal epoxidation, Δ^9-oxidative cleavage, and terminal modification to the required iodide. Condensation of triethyl phosphonoacetate with the all-trans C_{33} ketone followed by aluminum hydride reduction and manganese dioxide oxidation then effected a two-carbon extension to yield the necessary C_{35} side-chain aldehyde.

The quinones of the anaerobic photosynthetic bacterium, *Chlorobium thiosulfatophilum*, are unique in that the usual phytobacterial quinones, plastoquinone and ubiquinone, are supplanted by a family of menaquinones: menaquinone-7 (**1**), 1′-oxymenaquinone-7 (**3**), and 1′-oxomenaquinone-7 (**5**).[3] The last quinone, which is apparently specifically associated with sulfide metabolism,[3b] was named chlorobiumquinone upon its initial isolation. At that time, the $C_{45}H_{62}O_2$ structure **7**, lacking the first methylene of the normal isoprenoid side chain, was assigned.[4] Subsequently a mass spectrum of chlorobiumquinone was obtained in which a molecular ion at *m/e* 662 revealed the necessity of insertion of a CO unit into the proposed structure **7**. Similar observations by other investigators led to suggestion of the 1′-oxomenaquinone-7 structure (**5**) for chlorobiumquinone.[3a] The vinyl quinone structure was conclusively eliminated by synthesis of **7** which, although deceptively similar to chlorobiumquinone in uv, ir, and nmr spectra, was obviously dissimilar when compared chromatographically or by mass spectrometry.[5] To confirm the 1′-oxomenaquinone-7 structure for chlorobiumquinone its synthesis was therefore undertaken and is now reported in detail. A preliminary communication of this work has appeared.[5]



1, $n = 6$; R, R = H, H
2, $n = 1$; R, R = H, H
3, $n = 6$; R, R = H, OH
4, $n = 1$; R, R = H, OH
5, $n = 6$; R, R = =O
6, $n = 1$; R, R = =O



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Of the various approaches to the synthesis of chlorobiumquinone which one can envisage, several of the more promising were tested in model studies using C_5 or C_{10} side chains to simplify the analysis. In theory, the most direct approach to a 1′-oxomenaquinone would be selective oxidation at C-1′ of the corresponding menaquinone, since many menaquinones are naturally available. The biosynthetic analogy in this approach is obvious and somewhat justified in view of the augmented yields of chlorobiumquinone obtained from an oxidative (acetone–aqueous potassium ferricyanide) extraction of the bacteria[4] and the observation of 1′-oxomenaquinone formation from 1′-oxymenaquinone *in vitro*.[3b]

Menaquinone-7 itself, however, proved stable to mild oxidants such as potassium ferricyanide. Since alkyl groups on quinones are resistant to oxidation, the quinone nucleus usually suffering oxidation first, more drastic oxidation can only proceed on a suitably protected hydroquinone; however, such a procedure raises the question of subsequent removal of the protecting groups. Complete aromatization of the nucleus would also have the effect of activating the 1′ position to oxidative attack, since it would become both benzylic and allylic, although considerable activation is necessary for favorable competition with the other less hindered benzylic position (2-methyl) as well as the allylic methyls and methylenes of the side chain.

A recently investigated oxidant, AgO, was particularly attractive in that under mildly acidic conditions various substituted toluenes can be oxidized to the corresponding aldehydes with improvement in yield if an activating group is ortho or para to the site of oxidation.[6] When this oxidant was applied to the dimethyl ether of menaquinol-1 (**8**), a relevant model for our studies, the anticipated mode of oxidation was not

(1) This research was supported in part by Grants AI-04888 and AM-13688 from the National Institutes of Health, U. S. Public Health Service.

(2) National Institutes of Health Predoctoral Fellow.

(3) (a) R. Powls, E. Redfearn, and S. Trippett, *Biochem. Biophys. Res. Commun.*, **33**, 408 (1968); (b) R. Powls and E. R. Redfearn, *Biochim. Biophys. Acta*, **172**, 429 (1969).

(4) B. Frydman and H. Rapoport, *J. Amer. Chem. Soc.*, **85**, 823 (1963).

(5) W. E. Bondinell, C. D. Snyder, and H. Rapoport, *ibid.*, **91**, 6889 (1969).

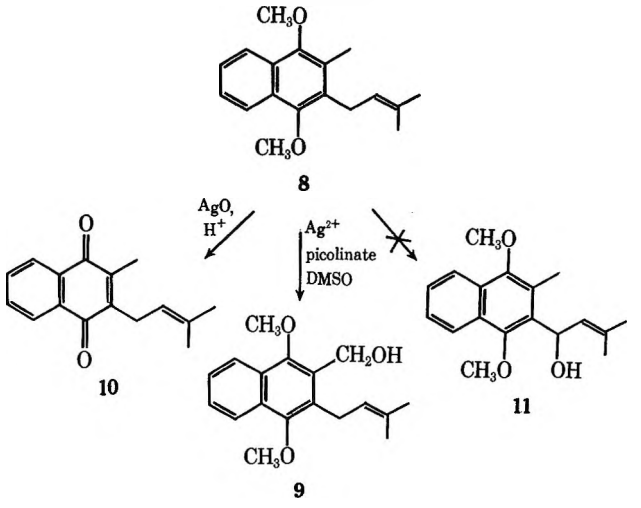
(6) L. Syper, *Tetrahedron Lett.*, 4193 (1967).

observed and, somewhat surprisingly, menaquinone-1 was the only product obtained. This previously unobserved oxidative demethylation reaction, which we will consider in detail in a future publication, has considerable import for quinone chemistry in that it allows protection as the hydroquinone methyl ethers. These groups are particularly stable to strongly anionic conditions and can then be removed by mild, selective oxidation. In fact, the further studies reported herein will make exclusive use of this protection–deprotection scheme.

Since acidic Ag^{2+} effected only demethylation, a nonacidic species, Ag^{2+} picolinate in DMSO, was then applied to **8** and an alcohol was obtained in 25% yield. Unfortunately, as confirmed by nmr and mass spectral analyses, oxidation occurred exclusively at the 2-methyl group, yielding benzyl alcohol **9**. Thus, at least chemically, selective oxidation is not a feasible method for 1′-oxomenaquinone synthesis (Scheme I).

SCHEME I

OXIDATION OF **8** WITH Ag^{2+} SPECIES



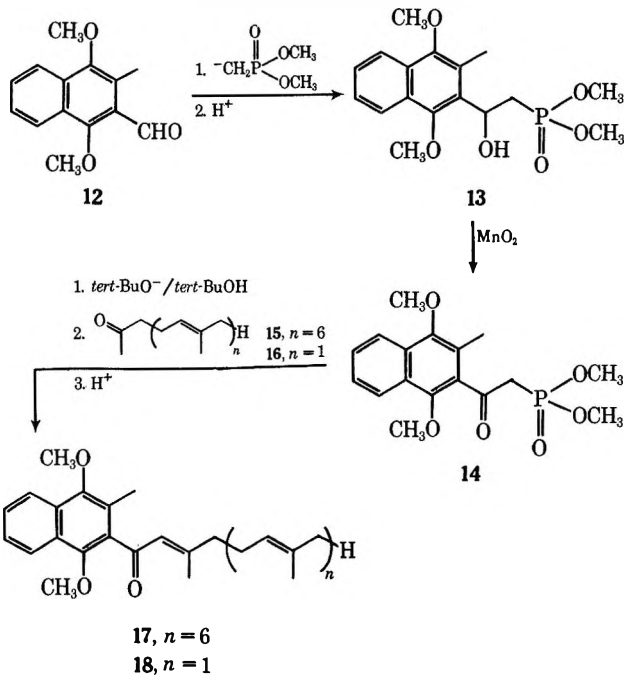
Chlorobiumquinone synthesis by bond formation at the $\Delta^{2'}$ position appears attractive especially if one considers reaction between β-ketophosphonate **14** and farnesylfarnesylacetone (**15**) in which the advantage is that the two carbon atoms necessary for completion of a C_{35} side chain are added to the naphthalenic nucleus rather than to the more valuable C_{33} side-chain component (Scheme II).

The required β-ketophosphonate **14** was derived in 75% yield from manganese dioxide oxidation of the corresponding β-hydroxyphosphonate **13**, which in turn was obtained (85% yield) by attack of the anion of methylphosphonic acid dimethyl ester[7] upon 2-methyl-3-formyl-1,4-dimethoxynaphthalene (**12**). Generation of **14** directly in the correct oxidation state by reaction with 2-methoxycarbonyl-3-methyl-1,4-dimethoxynaphthalene proved impossible because of hindrance about the ester. Formation of the anion of **14**, required for a Horner-type reaction, was then accomplished with potassium *tert*-butoxide in *tert*-butyl alcohol. However, reaction in the presence of 1 equiv of the C_8 ketone **16** for 1 week at 110° (conditions required for complete consumption of ketone) resulted in

(7) E. J. Corey and G. I. Kwiatkowski, *J. Amer. Chem. Soc.*, **88**, 5656 (1966), and references cited therein.

SCHEME II

PHOSPHONATE APPROACH TO SYNTHESIS OF **5**



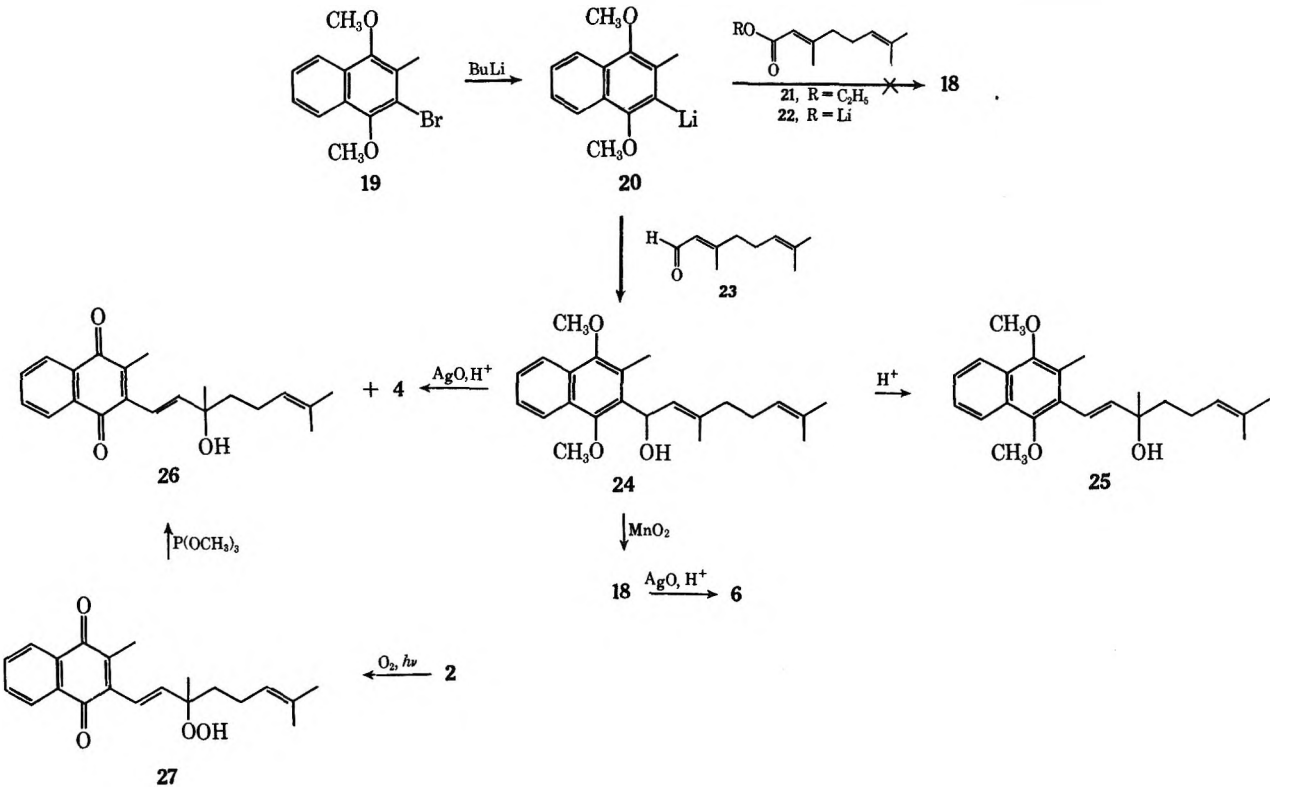
only a 7% yield of 1′-oxomenaquinol-2 dimethyl ether (**18**). Steric factors are obviously contributing to the low yield, and since the reaction with several other base–solvent systems gave even lower yields, the method was rejected as a resonable approach to chlorobiumquinone synthesis. This failure is interesting in that it demonstrates a limiting condition under which a β-ketophosphonate–ketone condensation can be considered useful.

The remaining approaches to 1′-oxomenaquinone synthesis involve addition of the side chain as a C_{35} unit. Acid-catalyzed electrophilic substitution of an α,β-unsaturated acyl chloride or an α,β-unsaturated aldehyde into the aromatic nucleus cannot reasonably be considered because of the inevitable simultaneous acid-catalyzed cyclizations of the polyunsaturated side chain. On the other hand, the anionic stability of the hydroquinone dimethyl ether suggested an alternative approach in which the organometallic nucleus, 2-lithio-3-methyl-1,4-dimethoxynaphthalene (**20**), could be condensed with a side-chain fragment leading directly or indirectly to the desired product. Reaction leading to product in the correct oxidation state, *i.e.*, by condensation with an α,β-unsaturated carboxylic acid derivative, is obviously preferable in that a step is saved, but condensation with an aldehyde fragment also is feasible since the resulting 1′-oxymenaquinol derivative should be easily oxidizable.

Formation of the desired lithio derivative **20** was first attempted by direct exchange of 2-methyl-1,4-dimethoxynaphthalene and butyllithium, but this was unsuccessful since quenching with D_2O gave no isotope incorporation. The alternative approach of transmetalation with 2-bromo-3-methyl-1,4-dimethoxynaphthalene (**19**) and butyllithium was employed. In order to test the reactivity of **20** with variously functionalized side-chain fragments, the ten-carbon α,β-unsaturated ester **21** was first conveniently synthesized by condensation of triethyl phosphonoacetate with 6-

SCHEME III

MODEL STUDIES LEADING TO 1′-OXOMENAQUINONE SYNTHESIS *via* 2-LITHIO-3-METHYL-1,4-DIMETHOXYNAPHTHALENE (20)



methyl-5-hepten-2-one (**16**). Reaction of the lithio reagent **20** with ester **21** yielded only a trace of condensation product; mostly recovered starting ester and 2-methyl-1,4-dimethoxynaphthalene were isolated. Extension of the reaction time did not lead to any improvement in yield, so that one can only assume that most of the lithio reagent **20** had been consumed by enolizable proton abstraction from the ester. Ester **21** was next hydrolyzed and the lithium salt of the corresponding acid **22** was obtained; again attack of **20** upon this salt did not occur. The next logical step would have been to utilize the acid chloride derived from **22** in which reactivity should have been sufficient. In anticipation of difficulties involved in preparing the long-chain, acid-sensitive fragment necessary for chlorobiumquinone, this approach was avoided and the similarly reactive α,β-unsaturated aldehyde **23** was tested instead.

As expected, citral (**23**) and 2-lithio-3-methyl-1,4-dimethoxynaphthalene (**20**) reacted immediately at room temperature to give allylic alcohol **24**, which was subjected to manganese dioxide oxidation to obtain the dimethyl ether of 1′-oxomenaquinol-2 (**18**) in 60% yield from citral (Scheme III). The resulting $\Delta^{2'}$ cis–trans mixture (cis:trans = 3:7) was easily separable by column chromatography on kieselgel, the cis isomer being eluted first. Vinyl methyl absorption in the trans isomer, located at δ 2.30 (d, J = 1 Hz), is distinctly separated from the corresponding methyl signal in the cis isomer, upfield at δ 1.92 (d, J = 1 Hz), as expected from the deshielding effect exerted by a carbonyl on a cisoid methyl group.

Conversion of hydroquinone dimethyl ether **18** to 1′-oxomenaquinone-2 (**6**) with acidic AgO led in about 50% yield to products which for the most part retained the stereochemistry about the $\Delta^{2'}$ position. Again the vinyl methyl signals were diagnostic: vinyl methyl absorption in the trans isomer at δ 2.24 (d, J = 1 Hz) and in the cis isomer at δ 1.93 (d, J = 1 Hz). As estimated by integration the trans isomer was contaminated with about 5% of the cis form whereas the cis isomer contained 15% trans. Cis–trans isomerization in this quinone series could be expected under mild conditions, especially in view of the lability of the $\Delta^{2'}$ position of menaquinone to isomerization even where conjugation to the chromophore is not involved.[8] As expected the uv spectra of the two quinones are almost superimposable [cis, λ_{max} 251 nm (ϵ 29,200), 265 sh (22,500), 325 (3600), and trans, λ_{max} 250 nm (ϵ 33,200), 265 sh (23,000), 325 (3800)].

If prior to MnO_2 oxidation the dimethyl ether of 1′-oxymenaquinol-2 (**24**) is subjected to AgO oxidative demethylation a mixture of two quinone alcohols is obtained without concomitant oxidation at C-1′. Isolated from the reaction in 26% yield, 1′-oxymenaquinone-2 (**4**) was resolved into its $\Delta^{2'}$ cis–trans components (cis:trans = 3:7) by tlc on kieselgel. These isomers were also distinguishable in their nmr spectra, with the vinyl methyl absorption of the cis isomer at δ 2.04 falling slightly downfield from the trans absorption at δ 2.00.

The uv spectrum of 1′-oxymenaquinone-2 (**4**) is qualitatively and quantitatively identical with the rather unique spectrum reported for 1′-oxymenaquinone-7 (**3**)[3b] in which the characteristic four-fingered absorption pattern of menaquinone is distorted by diminution of the conjugated quinone bands at 258 and 265 nm. Intramolecular hydrogen bonding, which might cause

(8) S. J. DiMari and H. Rapoport, *Biochemistry*, **7**, 2650 (1968).

such an effect, cannot be deduced from an ir comparison of 1′-oxymenaquinone-2 (**4**) and menaquinone-2 (**2**) since the two quinone carbonyls absorb identically at 1610 cm^{-1}. Unfortunately, 1′-oxymenaquinone-7 as isolated from the Chlorobacteria was characterized only by its tlc and uv properties, but comparison with the simpler isoprenolog, 1′-oxymenaquinone-2 (**4**), shows complete coincidence of properties, thus providing strong confirmatory evidence for the structure assigned this polar quinone.

In addition to 1′-oxymenaquinone-2 (**4**), another deep yellow, more polar (R_f 0.36) quinone was obtained from the above reaction in 34% yield. That this was the allylically rearranged trans quinone **26** was suggested by the uv similarity to other vinylnaphthoquinones [λ_{max} 250, 280 (sh), and 330 nm] and a low field vinyl hydrogen ($\Delta^{1'}$) singlet at δ 6.53 which is characteristic of this series.[9] Spectrometric comparison with authentic material obtained *via* reduction of the corresponding photohydroperoxide **27** conclusively established its identity.

A question remaining is at what stage in the AgO oxidation reaction did allylic rearrangement take place; *i.e.*, is the starting alcohol **24** rearranged with this equilibrium perpetrated upon oxidation, is the quinone product rearranged, or are both compounds liable to rearrangement? To test these possibilities the product quinones **4** and **26** were subjected separately to the oxidation conditions and after a 5-min exposure were recovered unchanged as assayed by tlc, establishing that within the time period of the reaction the quinones are completely stable to rearrangement. On the other hand, **24**, when subjected to the acidic solvent conditions minus AgO, was converted quantitatively into a new alcohol which by tlc was slightly more polar and more strongly uv absorbing than starting **24**. Nmr analysis confirmed that, as expected, the rearranged trans allylic alcohol **25** had been obtained. Evidence was a low-field vinyl AB quartet (δ 6.20 and 6.67, J_{AB} = 16 Hz) as well as a shift of the 3′-methyl absorption upfield to δ 1.38 (s) consistent with double bond migration. The strong uv absorption at 250 nm (ϵ 42,800) is also expected for the vinylnaphthalene chromophore.

This rearrangement was quantitative in less than a minute and the product quinones are stable to rearrangement; therefore, the fact that both rearranged and unrearranged quinone alcohols are obtained from the oxidation reaction can only reflect a rate competition between oxidation and rearrangement. Fortunately, the rates are close enough to allow isolation of both quinones and, although not investigated, factors such as acidity could probably be varied to obtain a product ratio favoring either isomer.

Since the model studies reported herein and as summarized in Scheme III provided a procedure for chlorobiumquinone synthesis, construction of the side chain was next undertaken.

Synthesis of the Side Chain.—Most syntheses of head-to-tail polyprenyl compounds proceed by repetition of a series of reactions which add one prenyl unit at a time to the growing chain. Some require separation of cis and trans isomers after each double bond is introduced to obtain all-trans geometry in the final product,[10a-d] while others are highly stereoselective and yield products with >90% trans content.[10e-n] We wished to proceed in a manner whereby head-to-tail polyprenyl compounds could be rapidly assembled from a few appropriately functionalized multiprenyl units. The Wittig reaction between multiprenyl ketones, *e.g.*, geranylacetone (**29**) and the masked functional ylide **40**, seemed the most promising approach for rapid assembly of such long-chain polyprenyl compounds, specifically ketones.[10o] This approach had been previously applied but the reactants, themselves prepared *via* the Wittig reaction, were mixtures of cis and trans isomers leading to products which contained only very small amounts of all-trans isomers.[10c]

To overcome these drawbacks, we planned our synthesis around the trans double bond of geraniol, which would remain intact throughout the chain assembly. Since a C_{33} ketone (**15**) was required initially, it was to be constituted from a C_{13} ketone and a C_{10} repeating unit, used twice. The C_{13} ketone was geranylacetone (**29**), in which the double bond is trans because of its origin from geraniol. The C_{10} repeating unit was to be derived from geranylacetone by masking the ketone, cleaving at the terminal double bond, and converting the new terminus to halide and then phosphonium salt. Thus the desired C_{10} unit would be available for Wittig reaction at one end and subsequent unmasking of the ketone function at the other, with its double bond trans and unaffected by the transformations.

By this plan, three of the five double bonds with stereochemistry in the final C_{33} ketone would be fixed as trans; the other two would be formed as cis–trans mixtures. Two separations would be necessary, and they should be easily effected by thiourea inclusion, since the C_{23} and C_{33} all-trans isomers have sufficient length to form stable complexes. On the other hand, complete rejection of the cis isomers should occur, since the cis double bond is situated well enough within the chain to result in a folded molecule.

Geranylacetone (**29**) was prepared as reported[11] from pure geraniol (**28**) (*ca.* 100% trans)[12] and was converted to the ethylene ketal **30** with ethylene glycol and *p*-toluenesulfonic acid in benzene. Ozonolysis of this ketal with 1 equiv of ozone either in methanol at −78° or in pentane (in the hope that monozonides

(9) (a) W. E. Bondinell, S. J. DiMari, B. Frydman, K. Matsumoto, and H. Rapoport, *J. Org. Chem.*, **33**, 4351 (1968); (b) C. D. Snyder and H. Rapoport, *J. Amer. Chem. Soc.*, **91**, 731 (1969).

(10) (a) A. Langemann and O. Isler, "Biochemistry of Quinones," R. A. Morton, Ed., Academic Press, New York, N. Y., Chapter 4; (b) J. W. Cornforth, R. H. Cornforth, and K. K. Mathew, *J. Chem. Soc.*, 2539 (1959); (c) G. I. Samokhalov and E. A. Obol'nikova, *Usp. Khim.*, **36**, 413 (1967); (d) M. Julia, S. Julia, and R. Guegan, *Bull. Soc. Chim. Fr.*, 1072 (1960); (e) E. J. Corey, J. A. Katzenellenbogen, and G. H. Posner, *J. Amer. Chem. Soc.*, **89**, 4245 (1967); (f) R. Zurfluh, E. N. Wall, J. B. Siddall, and J. A. Edwards, *ibid.*, **90**, 6224 (1968); (g) S. F. Brady, M. A. Ilton, and W. S. Johnson, *ibid.*, **90**, 2882 (1968); (h) E. J. Corey and J. A. Katzenellenbogen, *ibid.*, **91**, 1851 (1969); (i) E. J. Corey, H. Yamamoto, D. K. Herron, and K. Achiwa, *ibid.*, **92**, 6635 (1970); (j) W. S. Johnson, L. Werthemann, W. R. Bartlett, T. J. Brockson, T. Li, D. J. Faulkner, and M. R. Peterson, *ibid.*, **92**, 741 (1970); (k) D. J. Faulkner and M. R. Peterson, *Tetrahedron Lett.*, 3243 (1969); (l) R. J. Anderson, C. A. Henrick, and J. B. Siddall, *J. Amer. Chem. Soc.*, **92**, 735 (1970); (m) E. E. van Tamelen and J. P. McCormick, *ibid.*, **92**, 737 (1970); (n) B. M. Trost, *Accounts Chem. Res.*, **3**, 120 (1970). (o) For examples of procedures joining multiprenyl units in a head-to-head fashion, see J. F. Biellman and J. B. Ducep, *Tetrahedron Lett.*, 3707 (1969); E. H. Axelrod, G. M. Milne, and E. E. van Tamelen, *J. Amer. Chem. Soc.*, **92**, 2139 (1970); L. Werthemann and W. S. Johnson, *Proc. Nat. Acad. Sci. U. S.*, **67**, 1465 (1970).

(11) O. Isler, R. Ruegg, L. Chopard-dit-Jean, H. Wagner, and K. Bernhard, *Helv. Chim. Acta*, **39**, 897 (1956).

(12) A generous gift of Givaudan Corp.

would precipitate),[13] followed by reductive isolation using sodium borohydride,[14] gave 9-hydroxy-6-methyl-5-*trans*-nonen-2-one ethylene ketal (**36**). The ozonolysis was not selective[15] and 1,4-dihydroxypentane, 2-hydroxy-6-methyl-5-heptene, and 5-hydroxy-2-pentanone ethylene ketal were also formed, decreasing the yield of desired ketal **36** to 20–33% in this one-step process.

Alternatively, **36** was obtained from geranylacetone (**30**) in seven steps and 45% overall yield, selective epoxidation[16] of the terminal double bond being achieved initially *via* reaction with *N*-bromosuccinimide to the bromohydrin **31** followed by alkali to form the terminal epoxide **32**. The terminal epoxide structure for **32** was established by its nmr absorption which showed two methyls on an epoxide ring at δ 1.20 and 1.23, one vinyl methyl on a trans double bond at δ 1.64, and one α-epoxy proton at δ 2.62.[17,18]

In order to convert epoxide **32** to cleaved alcohol **36**, it was necessary to open the oxide ring to the glycol while leaving the ketal intact. For this reason, alkaline reagents.[19] were tried first, but glycol formation was slow and incomplete. Glacial acetic acid buffered with sodium acetate[20] hydrolyzed both epoxide and ketal; however, addition of acetic anhydride repressed ketal hydrolysis and the glycol monoacetate **33** was isolated in 77% yield. Its structure was established as the C-9 acetate by absorption at δ 1.18 for the gem-dimethyl and δ 4.8 for the acetoxy proton in the nmr. Treatment with methanolic potassium hydroxide gave the glycol **34** in which the C-9 proton absorption had shifted to δ 3.3. Oxidation with periodate than gave aldehyde **35**, and this was reduced with borohydride to alcohol–ketal **36**. the last three steps all proceeding in excellent yields.

To prepare the ketal phosphonium salt **39**, the alcohol was converted to iodide **38** *via* the tosylate **37**, and this was heated with triphenylphosphine to yield the semisolid phosphonium salt **39**. Attempts at crystallization from a number of solvents failed; acetone–benzene[10c] did yield crystalline material, but this had lost its ethylene ketal and was characterized as the ketophosphonium salt. Therefore the noncrystalline ketal-phosphonium salt **39**, which showed the requisite nmr absorption, was converted directly to the masked-functional ylide **40** in dimethyl sulfoxide using butyllithium.

Reaction of masked-functional ylide **40** with geranylacetone (**29**) followed by chromatography and molecular distillation gave some recovered **29** and an 88% yield of geranylgeranylacetone ethylene ketal (**41**) as a 3:2 cis–trans mixture at Δ^9 as indicated by glpc. No attempt was made to alter the isomer distribution in the Wittig reaction, and the isomers were separated by thiourea inclusion of the all-trans ketal from saturated methanolic thiourea, since this isomer now just exceeds the minimum length required for formation of a stable inclusion complex.[21] Configurational assignments made on the basis of this method of separation were confirmed by comparison of the nmr absorptions due to methyl groups on cis and trans double bonds at δ 1.66 and 1.60.[22] Deketalization with aqueous phosphoric acid in refluxing acetone gave *all-trans*-geranylgeranylacetone (**42**).

Repetition of this process, now using the ylide **40** and *all-trans*-geranylgeranylacetone (**42**) gave a 70% yield of farnesylfarnesylacetone ethylene ketal (**43**), again as a 3:2 cis–trans mixture at Δ^9. Separation of isomers and deketalization as previously led to *all-trans* farnesylfarnesylacetone (**15**), consistent with nmr, ir, and mass spectral data and homogeneous by tlc and glpc. This method for constructing long trans polyprenyl chains appears quite general and convenient; *e.g.*, a similar all-trans C_{15} masked-functional ylide unit could be prepared from farnesylacetone.

all-trans-Farnesylfarnesylacetone (**15**) was next condensed with the anion derived from triethyl phosphonoacetate to yield almost quantitatively the C_{35} ester **44**. Without further purification, this ester was subjected to lithium aluminum hydride reduction in the presence of aluminum chloride, giving C_{35} allylic alcohol **45** in 90% yield, which was directly oxidized with manganese dioxide to the C_{35} α,β-unsaturated aldehyde **46**. Purification by chromatography at this stage was particularly convenient and effective, giving **46** in 50% overall yield from **15**. A cis:trans ratio of 1:3 about the Δ^2 double bond was demonstrated in the nmr by separate aldehyde hydrogen absorptions at δ 9.85 (cis) and 9.90 (trans) (d, J = 8 Hz), and the 3-methyl absorption of the trans isomer at 2.13. These reactions leading to the synthesis of **46** are given in Scheme IV.

Synthesis of Chlorobiumquinone.—The next steps in chlorobiumquinone synthesis were performed exactly as in the model studies. Condensation of the side-chain aldehyde **46** with 2-lithio-3-methyl-1,4-dimethoxynaphthalene (**20**) proceeded quantitatively and the resulting allylic alcohol was immediately oxidized with manganese dioxide to give the dimethyl ether of 1′-oxomenaquinol-7 (**17**) in 60% yield from **46**. Separation of Δ^2 cis–trans isomers by chromatography was facile, the vinyl methyl (C-3′) absorption of the trans isomer being a diagnostic doublet (J = 1 Hz) at δ 2.20 while the corresponding signal of the cis isomer was

(13) J. A. Sousa and A. L. Bluhm, *J. Org. Chem.*, **25**, 108 (1960).

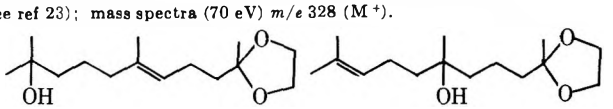
(14) C. G. Overberger and H. Kaye, *J. Amer. Chem. Soc.*, **89**, 5640 (1967).

(15) Compare the selective ozonolysis of geranyl acetate reported by (a) G. Stork, M. Gregson and P. A. Grieco, *Tetrahedron Lett.*, 1391 (1969), and (b) E. J. Corey, K. Achiwa and J. A. Katzenellenbogen, *J. Amer. Chem. Soc.*, **91**, 4318 (1969).

(16) E. E. van Tamelen and T. J. Curphey, *Tetrahedron Lett.*, 121 (1962); E. E. van Tamelen and K. B. Sharpless, *ibid.*, 2655 (1967). The conditions reported to selectively epoxidize the terminal double bond of geranyl acetate [M. Mousseron-Canet, M. Mousseron, and C. Levallois, *Bull. Soc. Chim. Fr.*, 297 (1964)] were not selective when applied to geranylacetone ethylene ketal.

(17) K. H. Dahm, B. M. Trost, and H. Roller, *J. Amer. Chem. Soc.*, **89**, 5292 (1967).

(18) The homogeneity of **32** was confirmed by reduction to i with lithium aluminum hydride in tetrahydrofuran [H. C. Brown, P. M. Weissman, and N. M. Yoon, *J. Amer. Chem. Soc.*, **88**, 1458 (1966)] and glpc of the trimethylsilyl ether. Comparison mixtures of i and ii were prepared by reduction of the monoepoxides obtained by *m*-chloroperbenzoic and peracetic acid oxidation (3:2) and by oxymercuration (9:1) of **30** followed by sodium borohydride reduction [H. C. Brown and P. Geoghegan, Jr., *ibid.*, **89**, 1522 (1967)]: R_T (as the trimethylsilyl ethers) for i, 18 min, and for ii, 20 min, column a (see ref 23); mass spectra (70 eV) m/e 328 (M^+).



i ii

(19) G. Berti, B. Macchia, and F. Macchia, *Tetrahedron*, **24**, 1755 (1968).

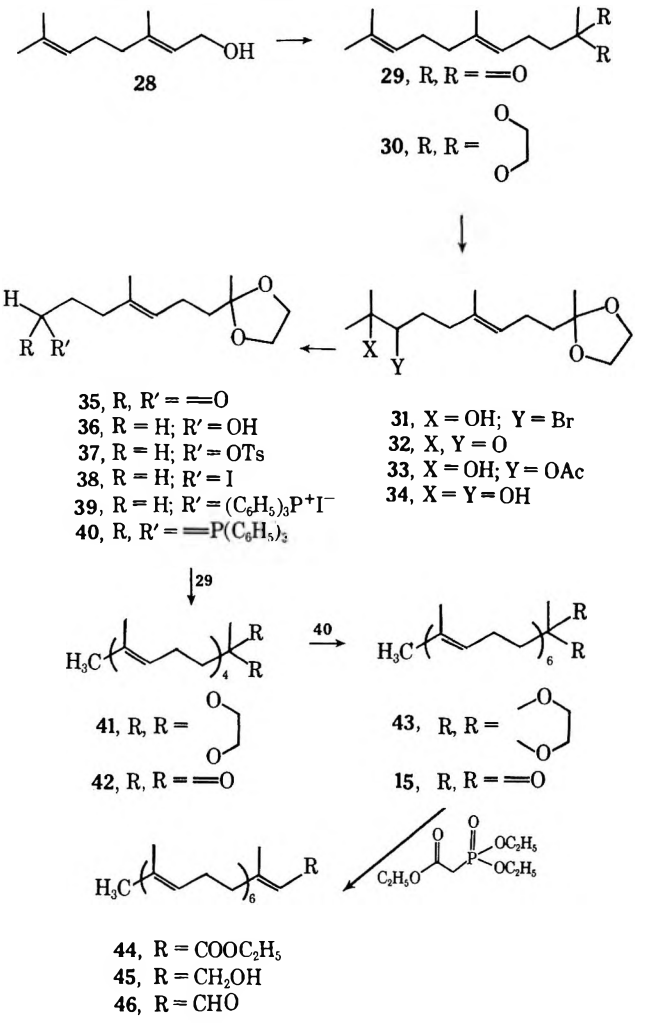
(20) E. E. Royals and J. C. Leffingwell, *J Org. Chem.*, **31**, 1937 (1966).

(21) R. W. Schliessler and D. Flitter, *J. Amer. Chem. Soc.*, **74**, 1720 (1952); D. L. Dare, I. D. Entwistle, and R. A. W. Johnstone, *J. Chem. Soc. C*, 977 (1968).

(22) J. W. K. Burrell, R. F. Garwood, L. M. Jackman, E. Oskay, and B. C. L. Weedon, *ibid.*, *C*, 2144 (1966).

SCHEME IV

SYNTHESIS OF C_{35}-MULTIPRENYL SIDE CHAIN



merged with methylene absorptions at 1.95. Separate oxidation of *cis*- and *trans*-**17** yielded *cis*- and *trans*-1′-oxomenaquinone-7 (**5**) in 55% yield. As judged by tlc using a chloroform–benzene (1:1) solvent system which resolves chlorobiumquinone into $\Delta^{2'}$-*cis*-(chlorobiumquinone-1) and -*trans*-(chlorobiumquinone-2)[3b] isomers, *trans*-**5** was prepared completely free of the cis isomer. On the other hand, *cis*-**5** was contaminated with *ca.* 10% of *trans*-**5**; however, by repeated preparative, tlc a pure sample of *cis*-**5** was obtained. After recrystallization from petroleum ether (bp 30–60°), *cis*-**5** and *trans*-**5** exhibited melting points of 42 and 50°, respectively, identical with those reported for the natural products.[3b]

The nmr spectra of *cis*- and *trans*-**5** shown in Table I are completely consistent with that originally reported for chlorobiumquinone[4] but somewhat at variance with a more recently presented spectrum.[3b] Apparently the quinone methyl signal has been incorrectly assigned[3b] to the methylene absorption region, thus confusing the quinone methyl with the vinyl methyl (C-3′) signal at δ 2.28. As anticipated from the model studies, the corresponding vinyl methyl absorption of *cis*-**5** is buried in methylene absorptions at δ 1.95.

The ultraviolet absorption spectra of synthetic *cis*- and *trans*-chlorobiumquinone (**5**) are almost superimposable and also identical with a redetermined spectrum of chlorobiumquinone, the extinctions reported[4] originally being in error: natural chlorobiumquinone, λ_{max} 250 nm (ϵ 31,000), 245 sh (30,200), 255 sh (30,100), 265 sh (21,800), 325 (3000); *trans*-**5**, 250 (32,000), 245 sh (31,000), 255 sh (31,000), 265 sh (22,000), and 325 (3000). Similarly the infrared and mass spectra were coincident with the natural material, thus confirming the structure of chlorobiumquinone as *all-trans*-1′-oxomenaquinone-7 by total synthesis.

Experimental Section[23]

2-Methyl-3-(3-methyl-2-butenyl)-1,4-dimethoxynaphthalene (8).—Menaquinone-1 (**10**)[24] (1.00 g, 4.17 mmol) was reduced in ethereal solution by shaking with aqueous hydrosulfite, and to the hydroquinone obtained after removal of solvent was added under nitrogen a KOH solution (4 g in 6 ml) and then dimethyl sulfate at room temperature. An oil formed after shaking with cooling for 10 min and the mixture was allowed to stand overnight. The product obtained by ether extraction of the dark brown mixture was chromatographed on kieselgel (eluent: 6% ether in petroleum ether) to yield starting quinone (111 mg) and menaquinol-1 dimethyl ether (**8**) as a colorless oil (700 mg, 70%): nmr δ 1.70, 1.83 [s, $=C(CH_3)_2$], 2.35 (s, $ArCH_3$), 3.53 (d, J = 6 Hz, $-CH_2-$), 3.85, 3.87 (s, OCH_3), 5.1 (t, J = 6 Hz, $-CH=$), 7.7 (m, ArH).

Anal. Calcd for $C_{18}H_{22}O_2$: C, 80.0; H, 8.2. Found: C, 79.7; H, 8.0.

Oxidation of Menaquinol-1 Dimethyl Ether (8) with Ag^{2+} Species. With AgO.—Menaquinol-1 dimethyl ether (**8**) (68 mg, 0.25 mmol), AgO[25] (496 mg, 4.00 mmol), dioxane (10 ml), and 85% H_3PO_4 (1 ml) were mixed and sonicated for 15 min. The product was isolated by partitioning between petroleum ether and water, and the crude product so obtained was chromatographed on kieselgel to yield menaquinone-1 (**10**) as a mobile yellow oil (41 mg, 69%), identical with authentic material.[24]

With Silver(II) Picolinate.—Menaquinol-1 dimethyl ether (**8**) (67 mg, 0.25 mmol), Ag^{2+} picolinate[26] (350 mg, 1.00 mmol), and DMSO (10 ml) were mixed and heated for 30 min at 80°, after which time the disappearance of the red color indicated consumption of the silver salt. Tlc (eluent: 90% ether in petroleum ether) showed some conversion to product in the polarity range (R_f 0.5) expected for an alcohol. The mixture was diluted with water and extracted with ether, and the combined ether extracts were washed with water and dried. The product mixture was chromatographed on kieselgel to yield starting material (20 mg) and a product (12 mg, 25% conversion) which by its nmr and mass spectrum was identified as 2-hydroxymethyl-3-(3-methyl-2-butenyl)-1,4-dimethoxynaphthalene (**9**): nmr δ 1.52, 1.72 [s, $=C(CH_3)_2$], 3.72 [d, J = 6 Hz, $-CH_2-$), 3.84, 3.92 (s, OCH_3), 5.05 (t, J = 6 Hz, $-CH=$), 5.60 (s, $-CH_2O$), 7.4, 8.0 (m, ArH); mass spectrum m/e 286 (M^+, 100), 272 (30), 269 (30).

2-Formyl-3-methyl-1,4-dimethoxynaphthalene (12).—2-Chloromethyl-1,4-dimethoxy-3-methylnaphthalene[27] (12.8 g, 51 mmol) was added to a solution of potassium *tert*-butoxide in *tert*-butyl alcohol (8.3 g, 212 mg-atoms of potassium in 800 ml) and then freshly distilled 2-nitropropane was added (21.7 g, 244 mmol). A white suspension of the salt formed and the reaction

(23) All melting points are uncorrected; microanalyses were performed by the Analytical Laboratory, University of California, Berkeley; uv absorptions were measured in isooctane; and nmr spectra were obtained on an A-60 Varian Associates instrument in deuteriochloroform unless otherwise stated with internal TMS (δ 0). All evaporations were *in vacuo* using a Berkeley rotary evaporator and all reactions were carried out in a nitrogen atmosphere. Chromatography was performed on Merck silica gel (60–80 mesh) or Camag kieselgel (>250 mesh) as specified. Glpc analyses were performed on (a) 30% QF-1 on acid-washed, DMCS-treated, 60–80 Chromosorb P, 10 ft × 0.25 in.; (b) 20% Carbowax 20M on 60–80 Firebrick, 10 ft × 0.25 in.; (c) Apiezon J on 60–80 Chromosorb P, 5 ft × 0.25 in.; (d) Apiezon L, capillary column, 100 ft × 0.1 mm.

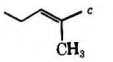
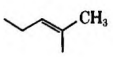
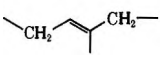
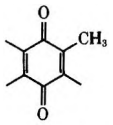
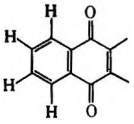
(24) O. Isler, R. Ruegg, A. Studer, and R. Jurgens, *Z. Physiol. Chem.*, **295**, 290 (1953).

(25) R. N. Hammer and J. Kleinberg, *Inorg. Syn.*, **4**, 12 (1953).

(26) E. G. Cox, W. Wardlaw, and K. C. Webster, *J. Chem. Soc.*, 775 (1936).

(27) L. I. Smith, S. Wawzonek, and H. C. Miller, *J. Org. Chem.*, **6**, 229 (1941).

TABLE I
NMR SPECTRAL COMPARISON OF CHLOROBIUMQUINONE AND SYNTHETIC 1'-OXOMENAQUINONE-7 (5) IN $CDCl_3$

Structure element	Chlorobiumquinone assignments, δ— 60 MHz[a]	220 MHz[b]	Synthetic 1'-oxomenaquinone-7 assignments (60 MHz), δ— *all-trans*-5	$\Delta^{2'}$-Mono-*cis*-5
	1.6 (br)	1.58 (s)	1.58 (s)	1.57 (s)
	1.7 (s)[d]	1.66 (s)	1.64 (s)	1.65 (s)
	2.0 (br)	1.99–2.08 (m)	1.95 (br)	1.95 (br)
	2.1 (s)	2.28 (s)	2.08 (s)	2.02 (s)
	2.3 (d)	2.22 (br)	2.28 (d, J = 2 Hz)	
	5.1 (br)	5.08 (br)	5.05 (br)	5.05 (br)
	6.2 (br)	6.15 (s)	6.15 (b, s)	6.02 (br, s)
	7.9 (m)	7.73, 8.06 (br)	7.7, 8.0 (m)	7.6, 7.9 (m)

[a] Reference 4. [b] Reference 3b. [c] In chain and terminal cisoid methyls. [d] Incorrectly reported[4] as a doublet.

was stirred at room temperature for 36 hr. The solvent was then removed *in vacuo* and the product was distributed between ether and water to remove acetone oxime and the last traces of solvent. Crude product obtained from the ethereal extract was then sublimed at 75° (10 μ) to give the aldehyde (10.8 g, 92%) as a white, crystalline product: mp 88°; glpc (column a) at 175° gave one peak, R_T 2.5 min; nmr 2.57 (s, $ArCH_3$), 3.80, 4.01 (s, OCH_3), 7.5, 8.1 (m, ArH), 10.58 (s, CHO).[9a]

Dimethyl 2-(1,4-Dimethoxy-2-methyl-3-naphthyl)-2-oxyethylphosphonate (13).—Dry THF (15 ml) was placed in one side of a double erlenmeyer flask along with dimethyl methylphosphonate[28] (645 mg, 5.2 mmol) while butyllithium (2.95 ml, 4.8 mmol) was placed in the other side. The solutions were cooled in Dry Ice–acetone and then mixed; aldehyde **12** (1.00 g, 4.35 mmol) was dissolved in dry THF (10 ml) and added to the now empty side. After cooling, the two solutions were mixed. After 15 min at −78°, the flask was allowed to warm to room temperature and the product solution was added to 2 N H_2SO_4, which was then extracted with chloroform. The chloroform extracts were washed with water, dried, and evaporated. Crude product was chromatographed on kieselgel (eluent: 15% methanol in benzene) to yield white, crystalline phosphonate **13** (1.33 g, 87%): mp 117°; nmr δ 2.56 (s, $ArCH_3$), 3.60 (q, J_{H-H} = 5 Hz, J_{P-H} = 22 Hz, $-CH_2P$), 3.83 (d, J = 11 Hz, $POCH_3$), 3.76, 3.92 (s, $ArOCH_3$), 4.70 (m, –CHOH–), 7.4, 8.0 (m, ArH).

Anal. Calcd for $C_{17}H_{23}O_6P$: C, 57.6; H, 6.5. Found: C, 57.7; H, 6.6.

Dimethyl 2-(1,4-Dimethoxy-2-methyl-3-naphthyl)-2-oxoethylphosphonate (14).—The hydroxy phosphonate **13** (650 mg, 1.84 mmol) was dissolved in chloroform (25 ml) and refluxed for 4 hr with active manganese dioxide. The MnO_2 was removed and the solvent was evaporated *in vacuo* to yield crude product (478 mg) which was chromatographed on kieselgel to yield pure keto phosphonate **14** (450 mg, 75%) as a viscous, light yellow oil: nmr δ 2.37 (s, $ArCH_3$), 3.62 (d, J_{P-H} = 11 Hz, $POCH_3$), 3.74 (d, J_{P-H} = 22 Hz, $-CH_2P$), 3.76, 3.79 (s, $ArOCH_3$), 7.4, 8.0 (m, ArH).

2-Methyl-3-(1-oxo-3,7-dimethyl-2,6-octadienyl)-1,4-dimethoxynaphthalene (18).—Keto phosphonate **14** (306 mg, 0.87 mmol), 6-methyl-5-hepten-2-one (127 mg, 1.00 mmol), potassium *tert*-butoxide in *tert*-butyl alcohol (0.83 mmol in 0.83 ml), and *tert*-butyl alcohol (4 ml) were mixed and heated at 110° for 1 week in a sealed tube. The reaction mixture was then partitioned between ether and water and the crude product (330 mg) obtained from the ether layer was chromatographed on kieselgel (eluent: benzene) to yield two bands which were *cis*- (3.3 mg) and *trans*- (3.5 mg) **18**: mass spectrum *m/e* (rel intensity) 352 (M^+, 20), 253 (20), 229 (100), 171 (15), 112 (20), 70 (75), 55 (50), identical for *cis*- and *trans*-**18**.

3,7-Dimethyl-2,6-octadienoic Acid (22).—Ethyl 3,7-dimethyl-2,6-octadienoate (**21**)[29] (1.82 g, 9.3 mmol) was suspended in 1 N NaOH solution (50 ml), and methanol (5 ml) was added. The solution was refluxed for 3 hr and after cooling was extracted with benzene to yield some recovered starting material (200 mg). The aqueous solution was acidified and then extracted again with benzene. The benzene extracts were distilled to remove residual water and then evaporated to yield pure acid **22** as a viscous, colorless oil: yield 1.25 g (90%); nmr δ 1.62, 1.68 [s, $=C(CH_3)_2$], 2.17 [d, J = 2 Hz, $=C(CH_3)-$], 5.07 (t, –CH=), 5.66 (b, COCH=).

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.4; H, 9.6. Found: C, 71.1; H, 9.4.

Reactions with 2-Lithio-3-methyl-1,4-dimethoxynaphthalene (20). A. Preparation of 20.—2-Bromo-3-methyl-1,4-dimethoxynaphthalene (**19**)[30] (281 mg, 1.00 mmol) was dissolved in ether (2 ml), and addition of butyllithium in hexane (0.62 ml, 1.00 mmol) led to a white precipitate. Water was added and the products in the ether layer were examined by nmr. Complete conversion to 2-methyl-1,4-dimethoxynaphthalene (δ 6.40, ArH) indicated that the organolithium compound **20** had been formed quantitatively.

B. Reaction of 20 with Ester 21.—To **20**, prepared as above, was added ester **21** (198 mg, 1.00 mmol). After 0.5 hr the reaction mixture was partitioned between ether and 2 N H_2SO_4 and evaporation of the ether followed by tlc indicated only starting ester, 2-methyl-1,4-dimethoxynaphthalene, and a trace of product

(28) A. H. Ford-Moore and J. H. Williams, *J. Chem. Soc.*, 1465 (1947).

(29) H. Machleidt, V. Hartmann, and H. Bunger, *Justus Liebigs Ann. Chem.*, **667**, 35 (1963).

(30) R. Adams, T. A. Geissman, B. R. Baker, and H. M. Teeter, *J. Amer. Chem. Soc.*, **63**, 528 (1941).

18. Extending the reaction time to overnight gave the same result.

C. Reaction of 20 with the Lithium Salt of Acid 22.—**20** was prepared as above and to it was added acid **22** (168 mg, 1.00 mmol) dissolved in THF (2 ml) to which butyllithium (0.62 ml, 1.00 mmol) in hexane had been added. After 2 hr the reaction was examined as above and no product **18** could be detected by tlc.

D. Reaction of 20 with Citral (23).—**20** was prepared as above. After 10 min citral (152 mg, 1.00 mmol) was added and after another 10 min the reaction mixture was partitioned between ether and 2 *N* H_2SO_4. The crude product from the ether solution (350 mg) was examined by tlc (eluent: benzene), which indicated only a trace of starting materials and mostly product in the polarity range (R_f 0.1) expected for 2-methyl-3-(1-oxy-3,7-dimethyl-2,6-octadienyl)-1,4-dimethoxynaphthalene (**24**). Pure **24** (304 mg, 86%) was obtained as a viscous, colorless oil from column chromatography: nmr δ 1.53, 1.62 [s, $=C(CH_3)_2$], 1.72 (s, $-CH_2CH_2-$), 2.00 (trans), 2.15 (cis) [br s, $=C(CH_3)-$], 2.45, 2.47 (s, $ArCH_3$), 3.77, 3.86 (s, $ArOCH_3$), 5.0 (br t, $-CH=$), 5.63, 5.87 (q, J_{AB} = 7 Hz, $-CHOHCH=$), 7.3, 7.9 (m, ArH); mass spectrum *m/e* (rel intensity) 354 (M^+, 40), 336 (100), 235 (30), 229 (25), 69 (40), 41 (40).

Anal. Calcd for $C_{23}H_{30}O_3$: C, 77.9; H, 8.5. Found: C, 78.0; H, 8.6.

Oxidation of 1′-Oxymenaquinol-2 Dimethyl Ether (24) with Manganese Dioxide.—**24** (300 mg, 0.85 mmol) was oxidized with MnO_2 (1.5 g) by refluxing for 0.5 hr in chloroform. The MnO_2 was removed and crude product was chromatographed on kieselgel (eluent: 10% ether in petroleum ether) to yield cis ketone **18** (35 mg, 12%) and trans ketone **18** (128 mg, 43%), as colorless oils: nmr, cis, δ 1.67 [s, $=C(CH_3)_2$], 1.92 (d, J = 1 Hz, $=CCH_3-$), 2.25 (s, $ArCH_3$), 3.80 (s, $ArOCH_3$), 5.17 (t, J = 6 Hz, $-CH=$), 6.28 (br, $COCH=$), 7.4, 8.0 (m, ArH); trans, 1.60, 1.67 [s, $=C(CH_3)_2$], 2.20 (d, J = 1 Hz, $=CCH_3-$), 2.30 (s, $ArCH_3$), 3.83, 3.86 (s, $ArOCH_3$), 5.07 (t, J = 6 Hz, $-CH=$), 6.37 (br, $COCH=$), and 7.5, 8.1 (m, ArH); uv λ_{max}, cis, 222 nm (ϵ 40,200), 232 sh (37,000), 330 (1900); trans, 223 (42,400), 232 sh (39,400), 330 (2100); mass spectrum, see **18** above prepared from β-ketophosphonate **14** and 6-methyl-5-hepten-2-one.

Anal. Calcd for $C_{23}H_{28}O_3$: C, 78.4; H, 8.0. Found: cis, C, 78.3; H, 7.8; trans, C, 78.4; H, 7.9.

2-Methyl-3-(1-oxo-3,7-dimethyl-2,6-octadienyl)-1,4-naphthoquinone (6).—*cis*-1′-Oxomenaquinol-2 dimethyl ether (**18**) (30 mg, 0.085 mmol), AgO (42 mg, 0.34 mmol), 85% H_3PO_4 (0.1 ml), and dioxane (1 ml) were mixed and sonicated for 15 min. The product was distributed between petroleum ether and water and the residue from the evaporation of the petroleum ether phase was chromatographed to obtain *cis*-1′-oxomenaquinone **6** as a yellow oil (10 ml, 36%), although some decomposition occurred on chromatography. *trans*-**18** (30 mg) was similarly treated to obtain *trans*-**6** (11 mg, 40%). Nmr, cis, δ 1.68 [s, $=C(CH_3)_2$], 1.93 (d, J = 1 Hz, $=CCH_3-$), 2.03 (s, $ArCH_3$), 5.15 (t, J = 6 Hz, $-CH=$), 6.07 (br, $COCH=$), 7.7, 8.0 (m, ArH); trans, 1.60, 1.67 [s, $=C(CH_3)_2$], 2.08 (s, $ArCH_3$), 2.28 (d, J = 2 Hz, $=CCH_3-$), 5.07 (t, J = 6 Hz, $-CH=$), 6.15 (br, $COCH=$), 7.7, 8.0 (m, ArH); uv λ_{max}, cis, 251 nm (ϵ 29,200), 265 sh (22,500), 325 (3600); trans, 250 (33,200), 265 sh (23,000), 325 (3800).

Anal. Calcd for $C_{21}H_{22}O_3$: C, 78.2; H, 6.9. Found for cis: C, 77.9; H, 6.8. Found for trans: C, 78.0; H, 6.8.

Oxidation of 1′-Oxymenaquinol-2 Dimethyl Ether (24) with AgO.—Crude **24** (0.3 mmol), AgO (150 mg, 1.2 mmol), and dioxane were mixed and then 6 *N* HNO_3 (0.3 ml) was added. After stirring for several minutes, the crude product (98 mg), obtained by partitioning between benzene and water, was chromatographed (eluent: 40% ether in petroleum ether) to obtain first 1-oxymenaquinone-2 (**4**) and then 2-methyl-3-(3-oxy-3,7-dimethyl-1,6-octadienyl)-1,4-naphthoquinone (**26**) both as yellow oils.

4: nmr δ 1.62 [s, $=C(CH_3)_2$], 1.6–1.8 (m, $-CH_2CH_2-$), 2.00 (trans), 2.04 (cis) [s, $=C(CH_3)$], 2.20 (s, $ArCH_3$), 5.0 (br, $-CH=$), 5.43 (br s, $-CHOHCH=$), 7.6, 7.9 (m, ArH); uv λ_{max} 244 nm (ϵ 19,250), 249 (19,400), 258 (14,00), 265 sh (13,300), 326 (3300); mass spectrum *m/e* (rel intensity) 324 (M^+, 8), 306 (10), 241 (40), 225 (70), 199 (100), 171 (50).

Anal. Calcd for $C_{21}H_{24}O_3$: C, 77.9; H, 7.5. Found: C, 78.1; H, 7.7.

26: nmr δ 1.38 [s, $-C(OH)CH_3-$), 1.62, 1.66 [s, $=C(CH_3)_2$], 2.22 (s, $ArCH_3$), 5.1 (t, J = 7 Hz, $-CH=$), 6.55 (s, $-CH=CH-$), 7.6, 8.0 (m, ArH); uv λ_{max} 250 nm (ϵ 22,800), 280 sh (8330), 330 3700); mass spectrum *m/e* (rel intensity) 324 (M^+, 5), 306 (20), 291 (20), 281 (25), 266 (50), 225 (50), 198 (100).

Anal. Calcd for $C_{21}H_{24}O_3$: C, 77.9; H, 7.5. Found: C, 77.8; H, 7.8.

2-Methyl-3-(3-oxy-3,7-dimethyl-1,6-octadienyl)-1,4-naphthoquinone (26) also was obtained from 2-methyl-3-(3-hydroperoxy-3,7-dimethyl-1,6-octadienyl)-1,4-naphthoquinone (**27**)[9b] (30 mg, 0.088 mmol) upon reduction in methylene chloride solution with 1 equiv of trimethyl phosphite; pure **26** (22 mg, 75%) was obtained by chromatography.

Acid-Catalyzed Rearrangement of 1′-Oxymenaquinol-2 Dimethyl Ether (24).—Crude **24** (0.2 mmol) was dissolved in dioxane (2 ml) and 6 *N* HNO_3 (0.2 ml) was added. An aliquot taken after 1 min indicated (tlc) complete conversion to a slightly less polar alcohol. The reaction mixture was distributed between water and petroleum ether and the crude product so obtained was chromatographed (eluent: 30% ether in petroleum ether) to yield a colorless oil, 2-methyl-3-(3-oxy-3,7-dimethyl-1,6-octadienyl)-1,4-dimethoxynaphthalene (**25**) (50 mg, 65%): nmr δ 1.36 [s, $-C(OH)CH_3-$], 1.63, 1.67 [s, $=C(CH_3)_2$], 2.35 (s, $ArCH_3$), 3.72, 3.77 (s, $ArOCH_3$), 5.1 (t, J = 7 Hz, $-CH=$), 6.20 6.6. (q, J = 16 Hz, $-CH=CH-$), 7.3, 7.9 (m, ArH); uv λ_{max} 251 nm (ϵ 42,800), 298 (6080); mass spectrum *m/e* (rel intensity) 354 (M^+, 100), 336 (40), 305 (10), 271 (90), 69 (80).

Anal. Calcd for $C_{23}H_{30}O_3$: C, 77.9; H, 8.5. Found: C, 77.8; H, 8.9.

Similar treatment of vinylhydroxyquinones **4** and **26** gave no change.

Geranylacetone (29).—Pure geraniol (**28**)[12] was converted to geranyl bromide with phosphorus tribromide and pyridine in petroleum ether at $-10°$. The bromide was treated with ethyl acetoacetate and ethanolic sodium ethoxide at $-10°$ and then with aqueous sodium hydroxide at 80° to yield pure geranylacetone: glpc (column b) R_T 19 min (nerylacetone, R_T 17 min).

Anal. Calcd for $C_{13}H_{22}O$: C, 80.4; H, 11.4. Found: C, 80.2; H, 11.4.

When phosphorus tribromide in ether[31] at $-78°$ and then at room temperature was used to effect bromide formation the geranylacetone contained 5% of methylene isomers as determined by the nmr spectrum (methylene protons at δ 4.8). These isomers probably arise by dehydrohalogenation of tertiary bromides formed by addition of hydrogen bromide to the double bond.

Geranylacetone Ethylene Ketal (30).—Geranylacetone (**29**), 90 g, was dissolved in 400 ml of dry benzene, 40 g of ethylene glycol and 300 mg of *p*-toluenesulfonic acid were added, and the mixture was stirred and heated under reflux for 9 hr with removal of water. Aqueous sodium carbonate was added to the cooled reaction mixture, the benzene layer was separated, and the aqueous phase was washed with petroleum ether. The combined organic phases were washed, dried, and evaporated to give the ketal which was chromatographed on silica gel, eluting with benzene, yield 105 g (95%) of geranylacetone ethylene ketal (**30**), <99% pure by glpc (column b).

Anal. Calcd for $C_{15}H_{26}O_2$: C, 75.6; H, 11.0. Found: C, 75.5; H, 10.6.

Ozonolysis of Geranylacetone Ethylene Ketal (30).—A solution of 24 of geranylacetone ethylene ketal (**30**) in 150 ml of methanol was cooled to $-78°$, and ozone (0.16 mmol/min) was passed through the solution until 1 equiv had been consumed (613 min). The reaction mixture was added immediately to a stirred solution of 7.6 g of sodium borohydride and 6.4 g of sodium hydroxide in 20 ml of water and 50 ml of methanol maintained at 5°. The resulting solution was stirred overnight and then refluxed for 10 min, cooled, diluted with water, and extracted with methylene chloride. Washing and evaporating the methylene chloride extract gave 14 g of oil. Glpc (column a) and comparison with authentic samples showed the oil to consist of 2-hydroxy-6-methyl-5-heptene, R_T 1 min; 5-hydroxy-2-pentanone ethylene ketal, 1 min 30 sec; geranylacetone ethylene ketal (**30**), 15 min; and 9-hydroxy-6-methyl-5-*trans*-nonen-2-one ethylene ketal (**36**), 18 min. This oil was chromatographed on silica gel, eluting with ethyl acetate–benzene (1:9, then 1:4) to give recovered **30**, and **36** in 20–33% yields: nmr δ 1.62 (br s, 3, $=CCH_3$), 3.5 (t, J = 6 Hz, $-CH_2OH$).

Anal. Calcd for $C_{12}H_{22}O_3$: C, 67.2; H, 10.3. Found: C, 67.1; H, 10.3.

(31) R. B. Bates and J. H. Schauble, *Tetrahedron Lett.*, 1683 (1963).

Geranylacetone Ethylene Ketal 9,10-Oxide (32).—A solution of 4.76 g of geranylacetone ethylene ketal (**30**) in 200 ml of 70% aqueous glyme was placed in a water bath at 18–20° and a solution of 3.56 g of *N*-bromosuccinimide in 50 ml of 70% aqueous glyme was added over 40 min. The glyme was distilled from lithium aluminum hydride before use and the NBS was crystallized from hot water. The internal temperature rose to 24° during the addition and the homogeneous solution was stirred for 30 min, diluted with water, and extracted with methylene chloride. Evaporation of the methylene chloride gave 6.8 g of an oil which was dissolved in 100 ml of methanol, stirred for 1 hr with 2.24 g of potassium hydroxide dissolved in 10 ml of methanol, diluted with water, and extracted with methylene chloride. Washing and evaporating the combined methylene chloride extracts gave 5.6 g of an oil which was chromatographed on silica gel, eluting with ethyl acetate–benzene (1:9) to give 1.54 g (31%) of recovered **30**, and 2.75 g (79% yield) of geranylacetone ethylene ketal 9,10-oxide (**32**).

Anal. Calcd for $C_{15}H_{26}O_3$: C, 70.8; H, 10.3. Found: C, 70.8; H, 10.0.

Geranylacetone Ethylene Ketal 9,10-Diol (34).—Geranylacetone ethylene ketal 9,10-oxide (**32**), 4.85 g, was dissolved in a mixture of 45 ml of glacial acetic acid, 5 ml of acetic anhydride, and 5 g of anhydrous sodium acetate. The resulting solution was stirred for 48 hr at room temperature and then was added slowly to a stirred solution of 50 g of sodium carbonate dissolved in 1 l. of water. This alkaline solution was further diluted with water and extracted with methylene chloride, which was evaporated, and the residue was chromatographed on silica gel, eluting with ethyl acetate–benzene (1:4) to give 4.6 g (77%) of the 9-acetate ester **33** of diol **34**: nmr δ 1.18 [$C(CH_3)_2$], 2.08 (s, O_2CCH_3), 4.8 (br, AcOCH).

The 9-acetate ester **33** was dissolved in 150 ml of methanol containing 0.25 g of potassium hydroxide and the solution was refluxed for 1 hr. Dilution with water, extraction with methylene chloride, evaporation, and chromatography on silica gel, eluting with ethyl acetate–benzene (3:7), gave 3.44 g (87%) of geranylacetone ethylene ketal 9,10-diol (**34**): nmr δ 1.15 [$C(CH_3)_2$], 3.3 (br, HOCH).

Anal. Calcd for $C_{15}H_{28}O_4$: C, 66.1; H, 10.4. Found: C, 66.2; H, 10.2.

9-Oxo-6-methyl-5-*trans*-nonen-2-one Ethylene Ketal (35).—Geranylacetone ethylene ketal 9,10-diol (**34**), 3.4 g, was stirred with 6.7 g of sodium metaperiodate in 100 ml of 30% aqueous dioxane for 30 min in the dark followed by dilution with water, extraction with methylene chloride, evaporation, and chromatography on silica gel, eluting with ethyl acetate–benzene (1:9), to give 2.4 g (90%) of 9-oxo-6-methyl-5-*trans*-nonen-2-one ethylene ketal (**35**), nmr δ 10.45 (t, -CHO).

Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.9; H, 9.5. Found: C, 68.1; H, 9.6.

9-Hydroxy-6-methyl-5-*trans*-nonen-2-one Ethylene Ketal (36).—A solution of 2.1 g of 9-oxo-6-methyl-5-*trans*-nonen-2-one ethylene ketal (**35**) in 30 ml of absolute ethanol was added to 0.4 g of sodium borohydride in 20 ml of absolute ethanol and the solution was stirred for 1 hr at room temperature and then heated to reflux for 10 min. Dilution with water, extraction with methylene chloride, and evaporation gave 2.0 g (97%) of 9-hydroxy-6-methyl-5-*trans*-nonen-2-one ethylene ketal (**36**), identical with **36** obtained *via* ozonolysis of **6**.

9-Iodo-6-methyl-5-*trans*-nonen-2-one Ethylene Ketal (38).—To a solution of 10.6 g of 9-hydroxy-6-methyl-5-*trans*-nonen-2-one ethylene ketal (**36**) in 50 ml of dry pyridine, stirred and cooled to 5°, was added 15 g of *p*-toluenesulfonyl chloride. The reaction mixture was stirred for 3 hr, after which several milliliters of ice water was added while the internal temperature was kept below 10°. Water, 100 ml, was then added followed by extraction with methylene chloride, which was washed and evaporated leaving the tosylate **37**, nmr δ 3.9 (t, J = 6 Hz, $-CH_2OTs$).

The tosylate, dissolved in 100 ml of dry acetone containing 15 g of sodium iodide, was left for 24 hr at room temperature. Dilution with water, extraction with methylene chloride, evaporation, and chromatography on silica gel, eluting with ethyl acetate–benzene (1:9), yielded 14 g (86%) of 9-iodo-6-methyl-5-*trans*-nonen-2-one ethylene ketal (**38**), nmr δ 3.08 (t, J = 7 Hz, $-CH_2I$).

Anal. Calcd for $C_{12}H_{21}IO_2$: C, 44.5; H, 6.5; I, 39.2. Found: C, 44.4; H, 6.6; I, 39.2.

Triphenylphosphonium Salt of 9-Iodo-6-methyl-5-*trans*-nonen-2-one.—Triphenylphosphonium salt of 9-iodo-6-methyl-5-*trans*-nonen-2-one was obtained when the noncrystalline phosphonium salt **39** (below) was crystallized from hot acetone–benzene and then from hot acetone, mp 138–139.5°.

Anal. Calcd for $C_{28}H_{32}IOP$: C, 62.0; H, 6.0; I, 23.4. Found: C, 62.0; H, 6.0; I, 23.2.

***all-trans*-Geranylgeranylacetone Ethylene Ketal (41).**—A mixture of 20 g of sublimed triphenylphosphine and 20 g of 9-iodo-6-methyl-5-*trans*-nonen-2-one ethylene ketal (**38**) was stirred and warmed to 80°; after 14 hr a hard, glasslike solid gradually dissolved and stirring was resumed. After a total of 24 hr, tlc and glpc (column a) showed that iodide **38** had been consumed and to the mixture of phosphonium salt **39** and triphenylphosphine cooled to room temperature was added 175 ml of dimethyl sulfoxide and 1 equiv of butyllithium in hexane (37 ml, 1.7 *N*) to generate the ylide **40**. The solution was stirred for 1 hr, 12.2 g of geranylacetone (**29**) was added, and the resulting solution was stirred for 48 hr at room temperature and then diluted with water. Extraction with hexane, evaporation, and chromatography on silica gel, eluting with hexane–benzene (1:1) to separate triphenylphosphine followed by ethyl acetate–benzene (2:98) gave a mixture of recovered **29** and product. Short-path distillation at 70° (3 mm) removed 2.1 g (17% recovery) of **20** from the mixture. Further distillation at 110° (20 μ) gave 17 g (88%) of geranylgeranylacetone ethylene ketal (**41**). Glpc (column c) showed that the Δ^9 cis and trans isomers were present in the ratio of 3:2: R_T cis 60 min, trans 67 min.

Separation of the Δ^9 cis and trans isomers was effected by thiourea inclusion of the all-trans ketal from saturated methanolic thiourea by solution at room temperature and then cooling to 4°. The inclusion compound crystallized during the cooling and was filtered off and washed with saturated methanolic thiourea at 4°. The all-trans ketal was liberated by destruction of the inclusion compound with warm water and extracted into petroleum ether. Thus 16 g of the mixture was separated into 4.2 g of *all-trans*-geranylgeranylacetone ethylene ketal (**41**), 7 g of the Δ^9-mono-cis isomer, and 4.0 g of unresolved ketal.

***all-trans*-Geranylgeranylacetone (42).**—*all-trans*-Geranylgeranylacetone ethylene ketal (**41**), 4.2 g, was dissolved in 50 ml of acetone, and 4 ml of 50% aqueous phosphoric acid was added. The resulting solution was refluxed for 3 hr, diluted with water, and extracted with methylene chloride, which was washed and evaporated to yield the ketone. Chromatography on silica gel, eluting with ethyl acetate–benzene (2:98), gave 3.65 g (98% yield) of *all-trans*-geranylgeranylacetone (**42**), glpc (column c), R_T 31 min, identical with an authentic sample.[12]

***all-trans*-Farnesylfarnesylacetone Ethylene Ketal (43).**—A twofold excess of phosphonium salt **39** was dissolved in dimethyl sulfoxide and converted to ylide **40** as previously described. *all-trans*-Geranylgeranylacetone (**42**), 3.65 g, was added to the ylide solution and stirred for 48 hr at room temperature. Dilution with water, extraction with methylene chloride, and evaporation left a residue which was chromatographed on silica gel to give 4.1 (73% yield) of farnesylfarnesylacetone ethylene ketal (**43**). Glpc (column d) showed that the Δ^9 cis and trans isomers were present in the ratio of 3:2: R_T cis 215 min, trans 225 min.

The ketal was dissolved in 25 ml of saturated methanolic thiourea and the solution was cooled to 4° over several hours, leading to crystallization of the inclusion compound which was filtered, washed with cold, saturated methanolic thiourea, and decomposed with warm water. Extraction with hexane gave 1.6 g (39%) of *all-trans*-farnesylfarnesylacetone ethylene ketal (**43**). The filtrate from the crystallization yielded 2.4 g of pure Δ^9-mono-cis isomer.

***all-trans*-Farnesylfarnesylacetone (15).**—*all-trans*-Farnesylfarnesylacetone ethylene ketal (**43**), 1.6 g, was deketalized and purified by chromatography to yield 1.43 g (97%) of *all-trans*-farnesylfarnesylacetone (**15**): homogeneous by glpc (column d); mass spectrum (70 eV) m/e 466 (M^+).

Anal. Calcd for $C_{33}H_{54}O$: C, 84.9; H, 11.7. Found: C, 84.9; H, 11.8.

Ethyl 3,7,11,15,19,23,27-Heptamethyl-2,6,10,14,18,22,26-octacosaheptenoate (44).—A 1-ml centrifuge tube was filled with NaH (33 mg, 50% oil dispersion) and dry THF (0.5 ml). Triethyl phosphonoacetate (150 mg, 0.67 mmol) was added at −80° and the tube was allowed to slowly warm to room temperature, adding more THF (0.5 ml) to achieve partial solubilization. The reagent was then added to another 1-ml centrifuge tube containing *all-trans*-farnesylfarnesylacetone (**15**) (150 mg, 0.34 mmol) and the mixture was heated to 68° for 5 hr. Partitioning between petroleum ether (2 ml) and 1 *N* NaOH (0.5 ml) gave crude ester **44**: yield 170 mg; nmr δ 1.23 (t, J = 7 Hz, CH_3-

CH_2–), 1.57 (s, =CCH_3–), 1.93 (br, –CH_2CH_2–), 2.10 (d, J = 1 Hz, COC=CCH_3–), 4.03 (q, J = 7 Hz, CH_3CH_2), 5.03 (br, –CH=), 5.52 (br, COCH=).

3,7,11,15,19,23,27-Heptamethyl-2,6,10,14,18,22,26-octacosaheptenol (45).—$LiAlH_4$ (21 mg, 0.56 mmol) and $AlCl_3$ (12.3 mg, 0.092 mmol) were weighed into a 1-ml centrifuge tube and the above crude C_{35} ester (**44**) dissolved in ether (0.5 ml) was added at −70°. After 1 hr at −10°, the reaction mixture was decomposed with wet ether and then partitioned between saturated NH_4Cl solution and petroleum ether. The crude yield of alcohol **45** was 136 mg: nmr δ 1.58 (s, =CCH_3–), 1.95 (br, –CH_2-CH_2–), 4.00 (d, J = 6 Hz, OCH_2–), 5.04 (br, –CH=), 5.34 (t, J = 6 Hz, OCH_2CH=).

3,7,11,15,19,23,27-Heptamethyl-2,6,10,14,18,22,26-octacosaheptenal (46).—The C_{35} alcohol **45** (above) was dissolved in chloroform (2 ml), MnO_2 (0.5 g) was added, the solution was sonicated for 15 min, and another portion of MnO_2 and chloroform was added and the sonication repeated. The MnO_2 was extracted exhaustively with chloroform to yield crude aldehyde (122 mg, 90%), which was chromatographed on silica gel yielding pure α,β-unsaturated aldehyde **46** as a viscous oil (83 mg, 50% overall yield from **15**): nmr δ 1.58 (br, =CCH_3–), 1.96 (br, –CH_2CH_2–), 2.13 (d, J = 2 Hz, trans COC=CCH_3–), 5.03 (br, –CH=), 5.75 (d, J = 8 Hz, COCH=), 9.85 (cis), 9.90 (trans) (d, J = 8 Hz, –CHO).

Dimethyl Ether of 1′-Oxomenaquinol-7 (17).—A suspension of **20** was prepared from 2-bromo-3-methyl-1,4-dimethoxynaphthalene (53 mg, 0.19 mmol), butyllithium (0.116 ml, 0.19 mol), and ether (0.5 ml). The C_{35} aldehyde **46** (above) (83 mg, 0.17 mmol) was dissolved in ether (0.5 ml) and added to the lithium reagent. After 10 min at room temperature, the mixture was partitioned between 2 N H_2SO_4 (0.2 ml) and petroleum ether. The crude product (120 mg) was oxidized with MnO_2 (1 g) in chloroform (5 ml) without further purification by sonicating for 15 min and then refluxing for 1 hr. Extraction of the MnO_2 with ether gave crude hydroquinone (108 mg) which was chromatographed to yield *cis*-**15** (20 mg) and *trans*-**15** (49 mg): overall yield from **46** was 60%; nmr, *trans*-**15**, δ 1.58 (s, =CCH_3), 1.95 (br, –CH_2CH_2–), 2.20 (d, J = 1 Hz, COC=CCH_3–), 2.23 (s, $ArCH_3$), 3.80 (s, $ArOCH_3$), 5.03 (br, –CH=), 6.27 (br, COCH=), 7.4, 8.0 (m, ArH); uv, *trans*-**15**, λ_{max} 220 sh (44,000), 232 sh (40,400), 325 (2500).

Anal. Calcd for $C_{48}H_{38}O_3$: C, 83.2; H, 9.9. Found: C, 83.1; H, 9.9.

1′-Oxomenaquinone-7 (15).—*trans*-**15** (52 mg, 0.06 mmol) was dissolved in dioxane (1 ml), 85% H_2PO_4 (0.1 ml) and AgO (42 mg, 0.34 mmol) were added, and the mixture was sonicated for 15 min. Extraction with ether gave crude product (42 mg) which was chromatographed on kieselgel to obtain pure *all-trans*-**5** (22 mg, 55%), mp 50° after crystallization from petroleum ether. *cis*-**15** (20 mg) was similarly treated to obtain $\Delta^{2'}$-mono-*cis*-**5**, mp 42°. Nmr is in Table I; uv, *all-trans*-**5**, λ_{max} 250 nm (ϵ 32,000), 245 sh (31,000), 255 sh (31,000), 265 sh (22,000), 325 (3000); $\Delta^{2'}$-mono-*cis*-**5**, 250 (30,800), 245 sh (29,700), 255 sh (29,700), 265 (21,400), 325 (2900); ir (neat), *all-trans*-**5**, 2960, 2940, 2910, 2850, 1660, 1610, 1595 cm^{-1} (C=O); mass spectrum m/e (rel intensity) 664 (M^+ +2, 7), 662 (M^+, 2), 241 (44), 201 (57), 200 (65), 81 (44), 69 (100), identical for $\Delta^{2'}$-mono-cis and all-trans.

Anal. Calcd for $C_{46}H_{62}O_3$: C, 83.3; H, 9.4. Found ($\Delta^{2'}$-mono-cis and all-trans): C, 83.1; H, 9.3.

Registry No.—*cis*-**4**, 32247-28-2; *trans*-**4**, 32304-12-4; *all-trans*-**5**, 32247-29-3; 2-mono-*cis*-**5**, 32247-30-6; *cis*-**6**, 32247-31-7; *trans*-**6**, 32247-32-8; **8**, 32247-33-9; **9**, 32247-34-0; **12**, 47827-40-6; **13**, 32247-36-2; **14**, 32247-37-3; **15**, 32304-17-9; 2-mono-*cis*-**17**, 32304-13-5; *all-trans*-**17**, 32247-38-4; *cis*-**18**, 32247-39-5; *trans*-**18**, 32247-40-8; **22**, 459-80-3; *cis*-**24**, 32247-42-0; *trans*-**24**, 32247-43-1; **25**, 32247-44-2; **26**, 32247-45-3; **29**, 3796-70-1; **30**, 3796-62-1; **32**, 32247-48-6; **33**, 32247-49-7; **34**, 32367-44-5; **35**, 24183-02-6; **36**, 32247-51-1; **38**, 3790-61-2; **39**, 32247-53-3; **43**, 32304-14-6; 2-mono-*cis*-**44**, 32304-15-7; *all-trans*-**44**, 32247-54-4; 2-mono-*cis*-**45**, 32247-55-5; *all-trans*-**45**, 32304-16-8; 2-mono-*cis*-**46**, 32247-56-6; *all-trans*-**46**, 32247-57-7.

Synthesis and Properties of α-Cyanoamino Acids. α-Cyanoglycine, L-β-Cyano-β-alanine, and L-γ-Cyano-γ-aminobutyric Acid[1a]

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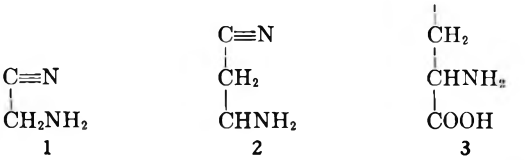
Received February 19, 1971

Syntheses of α-cyanoamino acids in the free state are reported for the first time. Enzymic deacylation of acetamidocyanoacetic acid gave α-cyanoglycine. *p*-Methoxybenzyloxycarbonyl-L-isoasparagine was dehydrated to *p*-methoxybenzyloxycarbonyl-L-β-cyano-β-alanine and treated with trifluoroacetic acid to give L-β-cyano-β-alanine. *p*-Methoxybenzyloxycarbonyl-L-isoglutamine was first converted to the methyl ester that was dehydrated and deprotected to give L-γ-cyano-γ-aminobutyric acid. Overall yields were 43–63%. Also synthesized were *p*-methoxybenzyloxycarbonyl-L-β-cyanoalanine, and, from it, L-β-cyanoalanine, and benzyloxycarbonyl-L-β-cyano-β-alanine and benzyloxycarbonyl-L-γ-cyano-γ-aminobutyric acid and their methyl esters. Characteristic physical properties and reactions of α-cyanoamino acids are given including hydration to amino acid amides and reductive cleavage of the cyano group as well as the kinetics of decomposition in aqueous solution.

Osteolathyrogens produce skeletal defects in experimental animals by inhibiting the maturation of collagen.[2] By contrast, the lathyrogens more recently isolated from legumes act as convulsants.[2] As part of an attempt to elucidate structure–activity relationships in the lathyrogens, it was desired to synthesize compounds that would incorporate structural features of both types. Such compounds would thus contain the α- or β-aminonitrile moiety of the osteolathyrogens, *viz.*, α-aminoacetonitrile (**1**) or β-aminopropionitrile (**2**), and the carboxyl group characterizing the neurolathyrogens, *viz.*, β-cyanoalanine (**3**). All these structural features

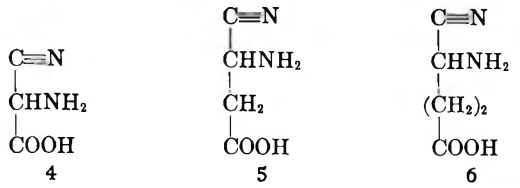


1 **2** **3**

would be present in α-cyanoamino acids such as α-cyanoglycine (**4**), L-β-cyano-β-alanine (**5**), and L-γ-cyano-γ-aminobutyric acid (**6**), a class of compounds

(1) (a) Aided by U. S. Public Health Service Grant NS 04316 and by Muscular Dystrophy Associations of America; (b) Visiting Research Fellow, 1967–1969; (c) 1964–1965; (d) 1961–1962.

(2) For reviews see K. A. Piez, *Annu. Rev. Biochem.*, **37**, 563 (1968); C. Ressler, *Fed. Proc.*, **23**, 1350 (1964).

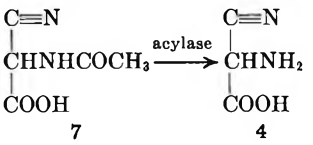


4 5 6

previously unavailable in the free state. It may be noted that L-β-cyano-β-alanine would be a structural isomer of L-β-cyanoalanine, the neurotoxic principle of *Vicia sativa* (common vetch),[3] and that L-γ-cyano-γ-aminobutyric acid would be a structural isomer of γ-cyano-α-aminobutyric acid, the neurotoxic product of cyanide fixation of *Chromobacterium violaceum*.[4] In the isomers the carboxyl and the cyano groups would remain approximately the same distance apart but the amino group would now be adjacent to the cyano rather than the carboxyl group.

The present paper describes the synthesis and properties of α-cyanoglycine, L-β-cyano-β-alanine, and L-γ-cyano-γ-aminobutyric acid. The three α-cyanoamino acids are strong inhibitors of bacterial L-glutamate decarboxylase,[5] an enzyme thought to modulate neuronal activity in higher species.

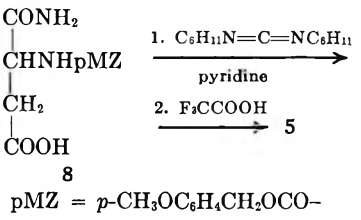
Syntheses.—Although free α-cyanoamino acids were not known, a variety of unisolated alkylated intermediates arising in the synthesis of amino acids by the acylaminocyanoacetic ester route were potentially useful precursors. For α-cyanoglycine commercial ethyl acetamidocyanoacetate served as the starting material. It was hydrolyzed in alkali to known acetamidocyanoacetic acid (**7**). The reported procedure[6] gave variable results in our hands. Frequently, from concentrated hydrolysis mixtures acidified to pH 1–2, a new substance crystallized out that analyzed interestingly as a hemipotassium salt of **7**. By further acidification to pH 0.5 it could be converted into **7**. Since it decarboxylates when heated in aqueous solution,[6] **7** was deacylated at 20° enzymically with hog kidney acylase.[7] The digest



7 4

was passed promptly through a column of CG-120 H^+ resin at 5°. Probably because of its acidic character, α-cyanoglycine appeared in early effluents but was retarded sufficiently to be freed of most of the salts in the digest. α-Cyanoglycine crystallized from the concentrated column effluents after addition of ethanol and was then recrystallized. Even though hydrolysis of **7** seemed to be largely asymmetric as judged by the yield of **4**, it is uncertain that the isolated α-cyanoglycine has the L configuration. Its specific rotation was close to 0. Moreover, carbethoxyacetamidoacetic acid in acid solution racemizes with a half-life at pH 3.85 of 20 min.[8]

An attempt to synthesize free β-cyano-β-alanine (**5**) by hydrogenolysis of *N*-benzyloxycarbonyl-L-β-cyano-β-alanine[9] was unsuccessful, although this procedure has preparative value for obtaining L-β-cyanoalanine and L-γ-cyanoaminobutyric acid from their *N*-benzyloxycarbonyl derivatives.[4] A variety of products formed; probably some reductive fission took place as it does with the Birch reagent.[9] The *p*-methoxybenzyloxycarbonyl (pMZ) protecting group removable under mild hydrolytic conditions[10] proved to be a more favorable approach in the route outlined as (1).



(1)

8

pMZ = *p*-$CH_3OC_6H_4CH_2OCO$–

pMZ-L-Isoasparagine (**8**) was dehydrated with *N*,*N*′-dicyclohexylcarbodiimide (DCCI) in pyridine[9,11] to pMZ-L-β-cyano-β-alanine. The latter was unusually susceptible to hydration back to the amide and it was desirable to treat the crude dehydration product directly with trifluoroacetic acid (TFA) to remove the protecting group. L-β-Cyano-β-alanine was then isolated by crystallization from water–ethanol in an overall yield of 50–60%. Such products usually contained 4–9% isoasparagine. Products having larger amounts of the latter were purified at 5° on a column of Dowex-1 (acetate) resin which retained only the slightly acidic cyanoamino acid.

pMZ-L-Asparagine likewise was dehydrated with DCCI in pyridine. pMZ-L-β-Cyanoalanine was isolated and then deprotected with TFA to give β-cyanoalanine that required little purification and was identical with authentic material.[11] Although this sequence was carried out on a microscale, it appears to offer a satisfactory alternate route to L-β-cyanoalanine[4,9,11–13] that avoids losses due to side reduction of the cyano group on hydrogenolysis of the benzyloxycarbonyl (Cbz) group.

The analogous route did not appear feasible for **6**. Although Cbz-L-glutamine is dehydrated to the γ-cyanoamino acid derivative with DCCI,[11] Cbz-L-isoglutamine[14] gave evidence of reaction but yielded no product having the expected acidic character.[15] Preparation of **6** was therefore undertaken by the route outlined as (2).

pMZ-L-Isoglutamine (**9**) was prepared by condensation of *p*-methoxylbenzyoxylcarbonyl azide (pMZ azide)[10] and L-isoglutamine[16] in the same manner as the asparagine compounds. Attempted liberation of **9** by acidification with 20% citric acid yielded largely an insoluble sodium salt that could be converted with 2 *N* HCl into **9** which was extractable. In both forms, **9** was esterified with diazomethane to give **10**. Treatment of **10** with the dehydrating agent dimethylform-

(3) C. Ressler, *J. Biol. Chem.*, **237**, 733 (1962).
(4) M. Brysk and C. Ressler, *ibid.*, **245**, 1156 (1970).
(5) C. Ressler and T. Koga, *Biochim. Biophys. Acta*, **242**, 473 (1971).
(6) N. F. Albertson, *J. Amer. Chem. Soc.*, **68**, 450 (1946).
(7) J. P. Greenstein, "Methods in Enzymology," Vol. 3, S. P. Colowick and N. O. Kaplan, Ed., Academic Press, New York, N. Y., 1957, p 558.
(8) S. G. Cohen and L. H. Klee, *J. Amer. Chem. Soc.*, **82**, 6038 (1960).
(9) C. Ressler and D. V. Kashelikar, *ibid.*, **88**, 2025 (1966).
(10) F. Weygand and K. Hunger, *Chem. Ber.*, **95**, 1 (1962).
(11) C. Ressler and H. Ratzkin, *J. Org. Chem.*, **26**, 3356 (1961).
(12) B. Liberek, Cz. Buczel, and Z. Grzonka, *Tetrahedron*, **22**, 2303 (1966).
(13) M. Wilchek, S. Ariely, and A. Patchornik, *J. Org. Chem.*, **33**, 1258 (1968).
(14) C. Ressler, *J. Amer. Chem. Soc.*, **82**, 1641 (1960).
(15) Recently instances were cited in which isoglutamine derivatives, related as potential precursors to thalidomide, on treatment with several dehydrating or peptide-forming agents cyclized to this glutarimide much more readily than the corresponding glutamine derivatives: Y. F. Shealy, C. E. Opliger, and J. A. Montgomery, *J. Pharm. Sci.*, **57**, 757 (1968).
(16) M. Bergmann and L. Zervas, *Chem. Ber.*, **65**, 1192 (1932).

TABLE I

SYNTHESES, PROPERTIES, AND ANALYSES OF α-CYANOAMINO ACID DERIVATIVES

Derivative	Scale, mmol	Reaction time, hr	Yield,[a] %	Crystn solvent[b]	Mp, °C	[α]D, in methanol
Cbz-L-β-Cyano-β-alanine methyl ester[c]	1	3	70, 54	A	60–61.5	$[\alpha]^{28}$ −35.7° (c 1.1)
Cbz-L-γ-Cyano-γ-aminobutyric acid methyl ester[d]	1.5	2.5	81, 35	B	51–52.5	$[\alpha]^{25}$ −47.8° (c 0.9)
pMZ-L-γ-Cyano-γ-aminobutyric acid methyl ester (11)[e]	4.5	1	79, 65	C	84.5–85.5	$[\alpha]^{24}$ −44.1° (c 1.1)
Cbz-L-β-Cyano-β-alanine	0.5	1.75	61, 32	B	88.5–90[f]	
Cbz-L-γ-Cyano-γ-aminobutyric acid[g]	0.5	.75	69, 47	B, C	110.5–112	$[\alpha]^{25}$ −49.7° (c 0.8)
pMZ-L-γ-Cyano-γ-aminobutyric acid (12)[h–i]	3.0	2.3	93	C	117–119	$[\alpha]^{24}$ −45.5° (c 1)

[a] Yield of crude and purified product melting within 1° of analytical material. [b] A, ether; B, ether–petroleum ether; C, ethyl acetate–petroleum ether. [c] *Anal.* Calcd for $C_{13}H_{14}N_2O_4$: C, 59.5; H, 5.38; N, 10.7. Found: C, 59.5; H, 5.32; N, 10.8. [d] *Anal.* Calcd for $C_{14}H_{16}N_2O_4$: C, 60.9; H, 5.84; N, 10.1. Found: C, 60.5; H, 5.86; N, 10.2. [e] *Anal.* Calcd for $C_{15}H_{18}N_2O_5$: C, 58.8; H, 5.92; N, 9.15. Found: C, 58.6; H, 6.07; N, 9.13. [f] Lit.[9] mp 87.5–89°. [g] *Anal.* Calcd for $C_{13}H_{14}N_2O_4$: C, 59.5; H, 5.38; N, 10.7. Found: C, 59.6; H, 5.38; N, 10.7. [h] *Anal.* Calcd for $C_{14}H_{16}N_2O_5$: C, 57.5; H, 5.52; N, 9.59. Found: C, 57.5; H, 5.58; N, 9.68. [i] Mass spectrum (70 eV) *m/e* (rel intensity) 292 (3) (p^+), 274 (1) ($p^+ - H_2O$), 265 (1) ($p^+ - HCN$), 230 (1) ($p^+ - COOH, - NH_3$), 223 (3), 219 (3), 210 (4), 203 (2) ($p^+ - COOH, - NH_3, - HCN$), 185 (7), 137 (42) ($CH_3OC_6H_4CH_2O$), 127 (8), 121 (100) ($CH_3OC_6H_4CH_2$), 109 (35) ($CH_3OC_6H_5$), 107 (18) ($C_6H_5CH_2O$), 94 (14), 91 (14) ($C_6H_5CH_2$), 84 (26), 77 (30) ($C_6H_5$), 55 (30) ($CHNH_2$-C≡N). [j] The acids showed small cyano bands and the esters, small or barely detectable cyano bands near 4.4 μ in ir.

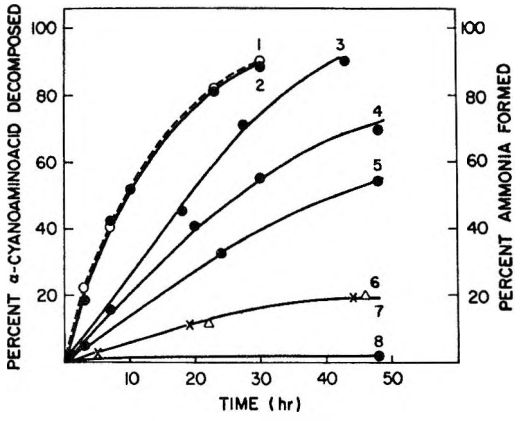
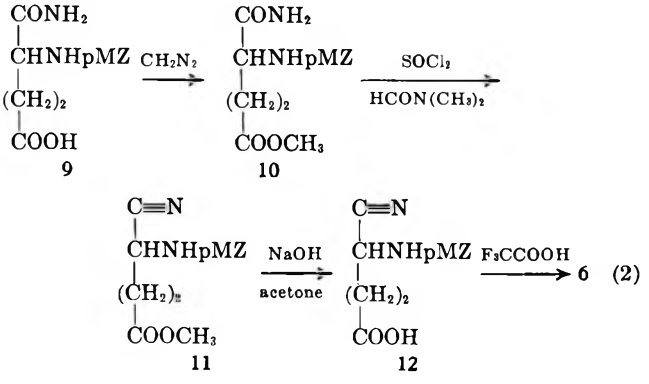


Figure 1.—Lability of α-cyanoamino acids in water: (2) L-γ-cyano-γ-aminobutyric acid at 36°; (5) at 25°; (3) L-β-cyano-β-alanine at 38°; (6) at 25°; (4) α-cyanoglycine at 38°; (7) at 25°; (8) L-β-cyanoalanine at 38°—all in 0.01 *M* solution (see Experimental Section). Release of ammonia during decomposition of γ-cyano-γ-aminobutyric acid at 36° is shown as 1 with the broken line. At the terminal periods for 2, 3, and 4, formation of free cyanide was 0.4, 7, and 12%.

amide–thionyl chloride[9,17] converted it in about 70% yield to pMZ-L-γ-cyano-γ-aminobutyric acid methyl ester (**11**) that was purified by recrystallization. This



was then hydrolyzed in the presence of 1 equiv of sodium hydroxide almost quantitatively to pMZ-L-γ-cyano-γ-aminobutyric acid (**12**). Deprotection gave in 75% yield crude L-γ-cyano-γ-aminobutyric acid (**6**) that was homogeneous on paper electrophoresis and required little purification. It was recrystallized from water–ethanol.[18]

As models for the latter dehydration route, the more accessible benzyloxycarbonyl derivatives were prepared. These included Cbz-L-isoglutamine methyl ester,[19] which was dehydrated to Cbz-L-γ-cyano-γ-aminobutyric acid methyl ester, that was hydrolyzed to Cbz-L-γ-cyano-γ-aminobutyric acid; and Cbz-L-isoasparagine methyl ester[17] which was dehydrated to Cbz-L-β-cyano-β-alanine methyl ester, that was hydrolyzed to Cbz-L-β-cyano-β-alanine. The latter agreed in melting point and ir spectrum with a sample of this material prepared by direct dehydration of Cbz-L-isoasparagine with DCCI.[9] Yields in each step were satisfactory and the new compounds were well characterized. Pertinent reaction conditions and results are summarized in Table I.

Properties—Purity of the three α-cyanoamino acids was established by elemental analysis, chromatography on the automatic amino acid analyzer,[20] and paper electrophoresis. The latter was particularly convenient for detecting the presence of isoasparagine and isoglutamine in **5** and **6**.

When stored in the solid state for several years in the cold under anhydrous conditions, the α-cyanoamino acids appeared to be stable. In dilute aqueous solution, however, they decomposed readily with the kinetics shown in Figure 1. To obtain these amino acids from aqueous solution, it is essential to isolate them promptly. γ-Cyano-γ-aminobutyric acid was the most unstable with a half-life at 36° of 9.5 hr. It decomposed with the formation of stoichiometric amounts

(17) H. Eilingsfeld, M. Seefelder, and H. Weidinger, *Angew. Chem.*, **72**, 836 (1960).

(18) Since this work was undertaken, **6** was reported to be an intermediate in glutamate biosynthesis for an unidentified basidiomycete, and it was synthesized in 1% yield by the Strecker reaction: G. A. Strobel, *J. Biol. Chem.*, **242**, 3265 (1967). The melting points and ir spectra of the natural and synthetic compounds, both of which were unanalyzed and obtained on only a 1-mg scale, differ from those of **6** synthesized here.

(19) E. Sondheimer and R. W. Holley, *J. Amer. Chem. Soc.*, **76**, 2467 (1954).

(20) D. H. Spackman, W. H. Stein, and S. Moore, *Anal. Chem.*, **30**, 1190 (1958).

of NH_3 (Figure 1). β-Cyano-β-alanine gave similar results with more scatter. No other ninhydrin-positive product was detected. In the decomposition of γ-cyano-γ-aminobutyric acid and β-cyano-β-alanine, presumably the amino group α to the cyano group is eliminated as NH_3. Little free cyanide was present in decomposition mixtures, and the other products, which may include cyanohydrins, remained to be elucidated.

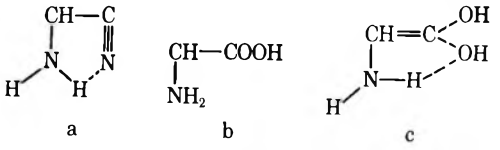
Despite their tendency to lose NH_3 in aqueous solution, β-cyano-β-alanine and γ-cyano-γ-aminobutyric acid hydrolyzed quantitatively in acid to the respective dicarboxylic acids, aspartic acid and glutamic acid, and 1 equiv of NH_3. α-Cyanoglycine gave 1 equiv of glycine and NH_3, presumably *via* decarboxylation and hydrolysis.

Hydrobromic acid–acetic acid hydrated β-cyano-β-alanine and γ-cyano-γ-aminobutyric acid almost quantitatively to isoasparagine and isoglutamine and appeared to decarboxylate α-cyanoglycine. This reaction was known to convert derivatives of β-cyanoalanine into asparagine compounds,[21] and it recently proved useful in identifying γ-cyano-α-aminobutyric acid isolated from certain culture filtrates of *Chromobacterium violaceum*.[4] It appears to be equally useful for characterizing α-cyanoamino acids of $n > 1$.

When treated with a slight excess of sodium in liquid ammonia, α-cyanoglycine gave glycine, L-β-cyano-β-alanine and its benzyloxycarbonyl derivative gave β-alanine, and L-γ-cyano-γ-aminobutyric acid and its benzyloxycarbonyl derivative gave γ-aminobutyric acid, all in yields of 90% or more.[22]

α-Cyanoglycine had the expected ir spectrum. Resembling L-β-cyanoalanine and L-γ-cyano-α-aminobutyric acid in the 4–5.5-μ range, it had a very sharp cyano band near 4.4 μ and a smaller, broader band at 4.9 μ that is attributed to the NH stretching vibration of the charged NH_3^+ group found in many amino acids.[23] By contrast, β-cyano-β-alanine and γ-cyano-γ-aminobutyric acid showed only a single small broad band at 4.5 and 4.6 μ (see Figure 2). It is uncertain if this band is a composite of the cyano and NH stretching vibration or if one of them is absent. In the ω-amino acids, β-alanine and γ-aminobutyric acid, NH stretching vibration is present near 5 μ.[23] When adjacent to an amino group that is separated from the carboxyl group by one or more methylene groups, the cyano group perhaps tends to suppress NH_3^+ formation. This possibility is consistent with the less polar nature of these amino acids suggested by their low melting points, which were all below 135°.

Mass spectra of the α-cyanoamino acids were obtained at low reservoir temperatures of 110–130°. As with EI spectra of most amino acids, the parent peak was absent or slight. Loss of carboxyl and HCN characterized their fragmentation. pMZ precursor 12 of γ-cyano-γ-aminobutyric acid showed a small parent ion and prominent expected aromatic fragments as well as loss of carboxyl and HCN. In all cases a very prominent ion was present at m/e 55; for α-cyanoglycine and β-cyano-β-alanine this was the base peak above m/e 50. The 55 peak may represent the fragment a, which might



a b c

be expected to be stable and may correspond to the less abundant masses 74 and 75 representing b and c of α-amino acids.[24] Its intensity may make the m/e 55 peak helpful in detecting the α-aminoacetonitrile structure.

Experimental Section[25]

Reductive fission was carried out by treatment of the sample (1–3 mg) in 2 ml of liquid NH_3 with a small excess of sodium. A few crystals of NH_4Cl were then added. The residue was taken up in water, adjusted to pH 2, and then determined on the amino acid analyzer. System C was used for β-alanine and γ-aminobutyric acid; system D for α-aminoacetonitrile.

Hydration was carried out by treatment of the sample (15–30 μmol) with 30–32% hydrobromic acid–acetic acid (Eastman) (25–50 μl) under anhydrous conditions for 15 min at room temperature. The mixture was frozen and lyophilized over P_2O_5 and KOH. The residue was dissolved in water, adjusted to pH 5, and determined on the analyzer.

Stability was examined in water in the presence of several drops of toluene in stoppered, 3-ml test tubes. Samples, taken

(21) M. Zaoral and J. Rudinger, *Collect. Czech. Chem. Commun.*, **24**, 1993 (1959).

(22) Reductive cleavage of the cyano group α to the amino group, in somewhat lower yields, had been observed previously in the analytical study[9] when dehydrated isoasparagine–oxytocin, dehydrated isoglutamine–oxytocin, and a few model compounds were treated with the Birch reagent. Although it is now clear that cleavage does not require methanol, when it is sought to distinguish the α-cyanoamino acid (isoasparaginyl and isoglutaminyl) from the ω-cyanoamino acid (asparaginyl and glutaminyl) structure, it may be desirable to include it in order to convert the ω-cyano group to the recognizable ω-aminomethyl group.[9]

(23) J. P. Greenstein and M. Winitz, "Chemistry of the Amino Acids," Vol. 2, Wiley, New York, N. Y., 1961, pp 1696–1705.

(24) K. Biemann and J. A. McCloskey, *J. Amer. Chem. Soc.*, **84**, 3192 (1962); G. Junk and H. Svec, *ibid.*, **85**, 839 (1963).

(25) Ethyl acetamidocyanoacetate was purchased from Aldrich Chemical Co., Milwaukee, Wis.; porcine kidney acylase, from Calbiochem, Los Angeles, Calif. *p*-Methoxybenzyl carbazate was prepared as described[10] and was also purchased from the Protein Research Co., Institute for Protein Research, Osaka University, Osaka City, Japan.

Infrared spectra were taken on a Perkin-Elmer Model 137 spectrophotometer on KBr disks containing 0.3% of sample. Medium, strong, and significant absorption bands are recorded. Mass spectra were obtained on a Hitachi Perkin-Elmer RMU-6E spectrometer. Samples were inserted into the direct inlet system at 110–140°. Elemental analyses were performed by Micro-Tech Laboratories, Inc., Skokie, Ill., and by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. Optical rotations were taken in a 2-dm cell in a Rudolph polarimeter, Model 80, or in a Rudolph photoelectric spectropolarimeter system, Model 80Q6-34402. Melting points were taken in capillaries and are corrected. Some varied with the rate of heating. Capillaries were inserted in a bath usually preheated to 30° below the melting point and heated at a rate of 2.5 or 3° per min. Dimethylformamide for amide dehydration was stored over Linde 4A Molecular Sieves. Evaporations were under reduced pressure unless otherwise indicated. Compounds liberated with HCl were washed on the filter until free of Cl^-. Acid hydrolyses were in 6 *N* HCl in sealed tubes under N_2 at 115° for 16 hr. AG 1-X4 resin (chloride, 100–200 mesh) was Dowex 1-X4 anion-exchange resin, analytical grade, purchased from Bio-Rad Laboratories, Richmond, Calif. The resin column was washed with 5 vol of 2 *N* sodium acetate until free of Cl^-, then with 2 vol of 0.5 *N* acetic acid, and, before use, with water until the effluent had pH 4.7.

Amino acid and ammonia analyses were performed on a Beckman–Spinco automatic amino acid analyzer, Model 120.[20] System A refers to the 150-cm resin column, pH 3.25 at 30° described for physiological fluids; system B, to the 50-cm column with type 50A resin at pH 4.26 and 30°; system C, at 50°; system D, the 15-cm column at pH 5.28 and 30°. Electrophoresis was on strips of Whatman No. 1 paper at 9–10 V/cm in sodium barbital buffer of pH 8.6 or pyridinium acetate buffer of pH 5.7 for 2.5 or 3 hr. Strips were sprayed with 0.15% ninhydrin in acetone and heated at 105°. Thin layer chromatography (tlc) was carried out on plates of silica gel G in system 1, *n*-butyl alcohol–acetic acid–5% NH_3 (11:6:3); system 2, *n* butyl alcohol–acetic acid–water (3:1:1); or system 3, *n*-propyl alcohol–concentrated NH_3 (67:33). For detection of pMZ derivatives, the plates were dried at 120° for 15 min and were then sprayed with dichromate–sulfuric acid and heated at 120° ("Thin-layer Chromatography, a Laboratory Handbook," E. Stahl, Ed., Academic Press, New York, N. Y., 1965, p 488). Ascending paper chromatography was on sheets of Whatman No. 1 paper in system 4, *n*-butyl alcohol–pyridine–acetic acid–water (15:10:3:12); in system 5, ethanol–concentrated NH_3–water (18:3:1), or descending in system 6, *n*-butyl alcohol–acetic acid–water (4:1:5).

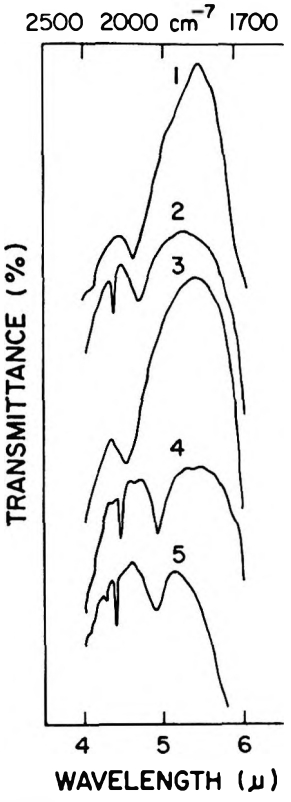


Figure 2.—Infrared spectra of α- and ω-cyanoamino acids in potassium bromide disks within 1700 and 2500 cm^{-1}; (1) L-γ-cyano-γ-aminobutyric acid; (2) L-γ-cyano-α-aminobutyric acid; (3) L-β-cyano-β-alanine; (4) L-β-cyanoalanine; (5) α-cyanoglycine.

at the times indicated in Figure 1, were placed directly on the analyzer, or frozen and analyzed soon after. For cyanide analysis, the solutions were kept in sealed ampoules and then placed in microdiffusion vessels. HCN was distilled into 1 *N* NaOH and determined as described.[5]

Acetamidocyanoacetic Acid Hemipotassium Salt.—Ethyl acetamidocyanoacetate, 34 g, was hydrolyzed as described[6] except that the reaction time was extended to 65 hr. The aqueous solution was concentrated to 30 ml, cooled, adjusted to pH 2 with concentrated HCl, and allowed to stand overnight in the cold. The white crystalline solid, wt 14.9 g (51%), mp 127–133°, was recrystallized from water–ethanol to give 8.32 g of clusters of needles, mp 133–134°, which was 2° below analytical material.

Anal. Calcd for acetamidocyanoacetic acid, $C_5H_6N_2O_3$ (142.1): C, 42.3; H, 4.26; N, 19.7. Calcd for potassium acetamidocyanoacetate, $C_5H_5N_2O_3K$ (180.2): C, 33.3; H, 2.79; N, 15.6. Calcd for acetamidocyanoacetic acid–potassium acetamidocyanoacetate, $C_5H_6N_2O_3 \cdot C_5H_5N_2O_3K$ (322.3): C, 37.3; H, 3.44; N, 17.4. Found: C, 37.3 (V_2O_5 used in combustion); H, 3.52; N, 17.8; neut equiv, 348 [determined by titration with 0.1 *N* NaOH (phenolphthalein)], 330 (electrometric).

Acid hydrolysis gave Gly, 1.04, and NH_3, 1.00, with quantitative recovery based on mol wt 322.

A solution of 300 mg in 1 ml of water was adjusted with 6 *N* HCl from pH 1.7 to pH 0.5. The solution became turbid and crystallization soon started, wt 135 mg, mp 110–112° dec. Recrystallization as for **7** raised the melting point to 114–115°. Admixture with **7** caused no depression in melting point.

Acetamidocyanoacetic Acid (7).—Ethyl acetamidocyanoacetate (17–34 g) was hydrolyzed as described[6] except that the pH of the concentrated aqueous solution was carefully adjusted to 0.5. The yield of crude product, mp 114–116°, was similar to that reported.[6] Recovery of unreacted ester was lower, however, making the overall yield 45–65%. Crude **7** was recrystallized by addition of ether and petroleum ether (bp 30–60°) to a solution in hot acetone and allowing it to stand at 25°.

α-Cyanoglycine (4).—A solution of 4.26 g (30 mmol) of **7** in 200 ml of distilled water was adjusted to pH 7 with 14.9 ml of 2 *N* LiOH. Porcine kidney acylase, 100 mg, 90 EU/mg, was added. The solution was stirred magnetically at room temperature and maintained at pH 7 by periodic addition of 1 *N* LiOH. Usually 13 ml was taken up within 1 hr, when 10 mg of enzyme was added. After a total of 2.5 hr, when 21 ml of base had been added, the uptake of base was slow. The solution was then stirred vigorously with 650 mg of activated charcoal and after 10 min, was filtered through a thin layer of wet charcoal. The yellow or red concentrate was adjusted to pH 1.9 with cold concentrated HCl and applied to a 1 × 50 cm column of Amberlite CG-120 H^+ resin maintained at 5°. The column was washed with water and the effluent was collected in fractions of several milliliters. These were tested for Cl^-, and for ninhydrin-reactive material by spot test on paper. The major ninhydrin-positive fractions, 7–14, were salt free and were immediately concentrated to a small volume. Crystallization started and was completed by addition of ethanol and cooling. After 30 min the product was collected on the filter, dried, and stored in the cold under vacuum, wt 1.14 g, mp 121.5° dec. Fractions 5 and 6, which contained some salt, yielded 0.55 g of Cl^--free product, mp 121° dec. α-Cyanoglycine of similar melting point could be obtained in comparable yield by crystallization without use of resin. Such products, however, frequently retained color or tended to darken.

For analysis a solution of 438 mg of crude α-cyanoglycine in 10 ml of water was treated with charcoal and was then diluted cautiously with 30 ml of ethanol. The colorless plates were collected, washed with ethanol and ether, and dried: wt 270 mg (63%); mp 124° dec; $[\alpha]^{24}D$ −0.05° (*c* 2, 1 *N* acetic acid); ir absorption at 3040, 2285 ($W_{1/2}$ = 0.04 μ), 2040 ($W_{1/2}$ = 0.23 μ), 1660, 1490, 1360, 1140, 1075, 934, 878, and 784 cm^{-1}; mass spectrum (70 eV) *m/e* (rel intensity) 113 (5), 112 (3), 73 (8) (p^+ − HCN), 55 (100) (p^+ − COOH, $CHNH_2C{\equiv}N$), 44 (136) (CO_2).

Anal. Calcd for $C_3H_4N_2O_2$: C, 36.0; H, 4.03; N, 28.0. Found: C, 36.3; H, 4.06; N, 27.8.

Paper electrophoresis at pH 8.6 gave a single purple-yellow ninhydrin spot 10 cm from the origin toward the anode: amino acid analysis in system A, elution vol 80 ml; ninhydrin color yield constant (*c*) 15.5.

***p*-Methoxybenzyloxycarbonyl-L-isoasparagine (8).**—L-Isoasparagine hydrate, prepared in quantitative yield by hydrogenolysis[16] of Cbz-L-isoasparagine,[26] was condensed with pMZ azide.[10] The general procedure of Weygand and Hunger[10] for the synthesis of pMZ amino acids was modified so that 2 mol of $NaHCO_3$ replaced MgO, 2 mol of pMZ azide were used, the reaction was run for 70 hr and reduced to half its volume, and the product was liberated with cold 6 *N* HCl (61%), mp 156°, $[\alpha]^{26}D$ −25.4° (*c* 1, dimethylformamide), with the expected elemental analysis. After it had been synthesized, **8** with the same optical rotation but lower melting point, 144–146°, was reported[27] as prepared by the general procedure.

***p*-Methoxybenzyloxycarbonyl-L-asparagine.**—Prepared from asparagine as described for **8**, this product agreed well in yield and properties with this compound prepared independently with pMZ azide and MgO[27] and recently by acylation with *p*-methoxybenzyl chloroformate.[28]

L-β-Cyano-β-alanine (5).—To a solution of 1.0 g of **8** in 6.8 ml of pyridine held at 19–21° was added with magnetic stirring over a period of 25 min a solution of 0.87 g of DCCI in 5.5 ml of pyridine. Stirring was continued for an additional 3 hr at 21–23°. The dicyclohexylurea was then filtered off and washed with pyridine, and the filtrate and washings were concentrated to a syrup at 1 Torr. The residue was taken up in 8 ml of 5% $NaHCO_3$, and the mixture was extracted with three 15-ml portions of ether. The aqueous layer was cooled and adjusted to pH 3 with 4 *N* HCl. The liberated oil was extracted with 32 ml of ether. The extract was washed with three small portions of water and dried ($MgSO_4$) for 3.5 hr in the cold. It was then concentrated at atmospheric pressure (bath 40–45°). The last few milliliters of solvent were removed with a current of dry N_2 at room temperature. To the liquid residue 0.67 ml of anisole was

(26) C. Ressler, H. Malodeczky, and D. V. Kashelikar, *Biochem. Prep.*, **10**, 83 (1963).

(27) E. Schröder and E. Klieger, *Justus Liebigs Ann. Chem.*, **673**, 208 (1964).

(28) S. Sakakibara, I. Honda, M. Naruse, and M. Kanaoka, *Experientia*, **25**, 576 (1969).

added. The mixture was cooled in an ice bath and cold TFA (3.7 ml) was added. The light pink solution was allowed to remain at 0° for 8 min and then was evacuated promptly at 0.025 Torr at 0° for 8 min. The residue was triturated twice with 10 ml of ether and was then dissolved in water and adjusted to pH 4.7 with 4 *N* NH_3. The solution was again extracted with ether and then concentrated. Ethanol was added and the mixture was stored in the cold. The crystalline solid was collected by filtration, washed with ethanol, and dried, wt 238 mg (overall yield 62%), mp 121.5–123° dec. It contained 96% **5** and 4% isoasparagine; similar products had 5–9% isoasparagine.

Earlier obtained products containing larger amounts of isoasparagine could be purified as follows. A solution of 700 mg in 11 ml of water was applied to a 44 × 1.5 cm column of AG 1-X4 (acetate) resin,[25] and the column was washed with water, all at 5°. At effluent volume 225 ml, pyridinium acetate buffer, pH 4.0 (15 ml of pyridine/1 l. of 1 *N* acetic acid), was substituted. Ninhydrin-positive material was present in fraction 1 (effluent volume 45–133 ml) and fraction 2 (66–159 ml after the change of eluent). Both fractions were concentrated almost to dryness and then were diluted with ethanol. The crystalline materials were collected and examined by paper electrophoresis at pH 5.7.[25] (In 2.5 hr, **5** travels 36 mm toward the anode; isoasparagine remains near the origin.) Fraction 1 yielded 222 mg, mp 116–118°, containing similar amounts of **5** and isoasparagine and presumably was material not adsorbed onto the column. Fraction 2 yielded 410 mg of **5**, mp 123–124° dec, having only a trace of isoasparagine.

For analysis 95 mg of **5** was dissolved in 1.8 ml of water at 25°, then diluted with alcohol and cooled: colorless needles; mp 122.5° dec; $[\alpha]^{26}D$ −12.1° (*c* 0.57, water); ir bands at 3040–2570 (b), 2220 ($W_{1/2}$ = 0.2 μ), 1645, 1575, 1520, 1410, 1335, 1298, 1150, 1063, 1020, 987, 972, and 714 cm^{-1}; mass spectrum (70 eV) *m/e* (rel intensity) 87 (51) (p^+ − HCN), 84 (24), 69 (52) (p^+ − COOH), 60 (23), 55 (100) ($CHNH_2C{\equiv}N$).

Anal. Calcd for $C_4H_6N_2O_2$: C, 42.1; H, 5.30; N, 24.6. Calcd for $C_4H_6N_2O_2$ containing 3.4% isoasparagine: C, 41.9; H, 5.33; N, 24.4. Found: C, 42.2; H, 5.41; N, 24.0.

Amino acid analysis in system B, elution vol 37 ml (*c* 24.5); 3.4% isoasparagine at 55 ml. In system A, elution vol 398 ml in the position of valine. In system C, 15–22% conversion to isoasparagine took place.

β-Cyanoalanine (3).—pMZ-L-Asparagine, 0.59 g, was treated with DCCI as described under **5**. The dried ether extract was concentrated to 10 ml and the product was precipitated with *n*-hexane and was reprecipitated in a similar way. Crude **pMZ-L-β-cyanoalanine**, 0.42 g (76%), mp 75–91° dec, was recrystallized from ether–petroleum ether (bp 30–60°): mp 93.5–94.5°; $[\alpha]^{25}D$ −13.8° (*c* 1, methanol); tlc R_{f1} 0.67, single spot; ir band at 2280 cm^{-1}.

Anal. Calcd for $C_{13}H_{14}N_2O_5$: C, 56.1; H, 5.07; N, 10.1. Found: C, 56.1; H, 5.16; N, 10.1.

Crude pMZ-L-βCNala, 0.137 g, was deprotected with 0.5 ml of TFA as described for **5**. The product in 0.5 ml of water at pH 5 was diluted with 2 vol of ethanol, wt 53 mg. Two recrystallizations yielded 30 mg (53%) of fine needles homogeneous on paper electrophoresis at pH 5.6 and showing 98.8% **3**[11] and 1.2% asparagine on amino acid analysis in system A. Admixture with **3**[11] caused no depression in melting point.

***p*-Methoxybenzyloxycarbonyl-L-isoglutamine (9).**[29]—Cbz-L-Isoglutamine was prepared by amidation of Cbz-L-glutamic anhydride[16] as modified by Shealy, *et al.*[15] For a large scale this was more convenient than the mixed anhydride procedure.[14] L-Isoglutamine, 7.24 g, obtained by hydrogenolysis of Cbz-L-isoglutamine, was treated with 20.5 g of pMZ azide and 8.33 g of $NaHCO_3$ as described for **8**. The concentrated aqueous layer, 80 ml, was cooled and acidified with 20% citric acid. The gelatinous precipitate was collected by filtration, wt 9.6 g. After two recrystallizations from ethanol this melted at 162.5–164.5° dec. It contained 7.1% residue (calcd for Na salt, 6.9%) and yielded 87% isoglutamine on hydrogenolysis. A suspension of 1.2 g in 30 ml of water was adjusted with 2 *N* HCl from pH 4.5 to pH 2. The solid was extracted with 100 ml of ethyl acetate. The dried ($MgSO_4$) extract yielded 0.95 g of residue melting at 118–123°. Two recrystallizations from tetrahydrofuran–petroleum ether raised the melting point to 127.5–130.5° dec, $[\alpha]^{26.5}D$ −5.5° (c 1.1, methanol).

Anal. Calcd for $C_{14}H_{18}N_2O_6$: C, 54.2; H, 5.85; N, 9.03. Found: C, 54.6; H, 6.05; N, 8.74.

***p*-Methoxybenzyloxycarbonyl-L-isoglutamine Methyl Ester (10).**—Crude **9** was extracted with hot ethanol, 40 ml per gram. The extract was filtered and gave 8.67 g of residue that was divided into three batches, each in 40 ml of methanol, and treated with a slight excess of diazomethane in ether for 10 min. The solutions were promptly filtered and taken to dryness. The combined product, 8.58 g, mp 104–108°, was recrystallized from methanol–water to give 6.51 g of needles, mp 117–119° (86%). Recrystallization raised the melting point to 119–120.5°, $[\alpha]^{24}D$ −5.5° (*c* 0.9, methanol).

Anal. Calcd for $C_{15}H_{20}N_2O_6$: C, 55.6; H, 6.22; N, 8.64. Found: C, 55.9; H, 6.42; N, 8.67.

Purified **9**, 70 mg in 5 ml of methanol, yielded 52 mg of **10** of the same melting point.

Methyl Esters of *N*-Benzyloxycarbonyl-L-β-cyano-β-alanine, *N*-Benzyloxycarbonyl-L-γ-cyano-γ-aminobutyric Acid, and *N*-*p*-Methoxybenzyloxycarbonyl-L-γ-cyano-γ-aminobutyric Acid (11).—Cbz-L-Isoasparagine methyl ester,[16] Cbz-L-isoglutamine methyl ester,[19] and pMZ-L-isoglutamine methyl ester (**10**) were starting materials. These were dehydrated with dimethylformamide–thionyl chloride as described previously with Cbz-L-asparagine methyl ester,[9] except that 3 mol of $SOCl_2$ per mol of amide were used. The reaction mixture of Cbz-L-γ-cyano-γ-aminobutyric acid methyl ester was processed in the cold room because of the low melting point of this product.

***N*-Benzyloxycarbonyl-L-β-cyano-β-alanine, *N*-Benzyloxycarbonyl-L-γ-cyano-γ-aminobutyric Acid, and *N*-*p*-Methoxybenzyloxycarbonyl-L-γ-cyano-γ-aminobutyric Acid (12).**—Cbz-L-β-Cyano-β-alanine methyl ester and **11** were dissolved in acetone–water (2:1), 1 mmol/ml, and 1 equiv of 1 *N* NaOH was added dropwise to maintain pH 8–9. Cbz-L-γ-Cyano-γ-aminobutyric acid methyl ester was dissolved in 0.5 ml of acetone and 1 equiv of 0.1 *N* LiOH was added initially. After the reaction periods indicated in Table I, the solutions were adjusted to pH 7 and acetone was evaporated off. The aqueous solutions were extracted with ethyl acetate and then acidified with 2 *N* HCl and extracted with ethyl acetate. For **12**, the solution was adjusted to pH 4.5 with 1 *N* citric acid. The ethyl acetate extracts were washed with water and dried ($MgSO_4$), and the solvent was removed. Table I gives the yields and properties of the acids and the foregoing esters.

L-γ-Cyano-γ-aminobutyric Acid (6).—Deprotection of 0.73 g (2.5 mmol) of **12** was carried out as described for **5**. When the residue freed of TFA was dissolved in 5 ml of cold water and was adjusted to pH 5, the product separated. The mixture was shaken several times with ether and then concentrated to 2.5 ml and cooled overnight. The solid was collected by centrifugal filtration, wt 240 mg (75%), mp 131–133° dec. Paper electrophoresis at pH 8.5 showed a single ninhydrin-positive spot. For analysis 115 mg was dissolved in 10 ml of water at 25° and the solution was diluted with 30 ml of ethanol and cooled. Recrystallized in the same way, the prisms melted at 134.5–136.5° dec: $[\alpha]^{24}D$ +25.3° (*c* 0.8, water) (lit.[18] mp 188–190°); ir bands at 3130–2440, 2175 ($W_{1/2}$ = 0.12 μ), 1640, 1540–1420, 1180, 1150, 1075, 1040, 1015, 990, 888, 798, and 743 cm^{-1}; mass spectrum (70 eV) *m/e* (rel intensity) 128 (4) (p^+), 111 (7) (p^+ − NH_3 or − OH), 101 (20) (p^+ − HCN), 83 (59) (p^+ − COOH), 74 (58) (CH_3CH_2COOH), 57 (100) (p^+ − COOH, − CN), 55 (62) ($CHNH_2C{\equiv}N$).

Anal. Calcd for $C_5H_8N_2O_2$: C, 46.9; H, 6.29; N, 21.9. Found: C, 46.6; H, 6.42; N, 21.8.

Amino acid analysis in system B, elution vol 100 ml, 7 ml before isoglutamine. A mixture of the two was separable; *c* 24.5; ratio 1.94 of the absorbance of the ninhydrin product at 570 and 440 mμ. Tlc: R_{f2} 0.42, R_{f3} 0.55; R_{f4} 0.51, R_{f5} 0.31.

Registry No.—**4**, 6232-21-9; **5**, 31883-83-7; **6**, 31883-84-8; **8**, 31883-85-9; **9**, 31883-86-0; **10**, 31883-87-1; **11**, 31883-88-2; **12**, 31883-89-3; Cbz-L-β-cyano-β-alanine methyl ester, 31883-81-5; acetamidocyanoacetic acid hemipotassium salt, 31883-90-6; pMZ-L-β-cyanoalanine, 31883-91-7; Cbz-L-γ-cyano-γ-amino, butyric acid methyl ester, 31883-92-8; Cbz-L-β-cyano-

(29) No attempt was made to improve the procedure. In future preparations it may be preferable to acidify directly to pH 2 with 2 *N* HCl instead of with 20% citric acid and extract the product.

β-alanine, 7436-73-9; Cbz-L-γ-cyano-γ-aminobutyric acid, 31883-94-0.

Acknowledgments.—The authors thank Dr. Paul M. Gallop and Mr. Edward M. Henson for the mass spectra, Dr. Tomohide Koga for the cyanide analyses, and Mrs. Harriet R. Levie and Miss Christine Lauinger for assistance with the stability studies.

2,4-Dimethoxybenzyl as a Protecting Group for Glutamine and Asparagine in Peptide Synthesis

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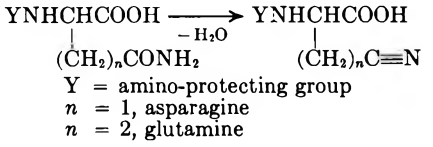
Received March 16, 1971

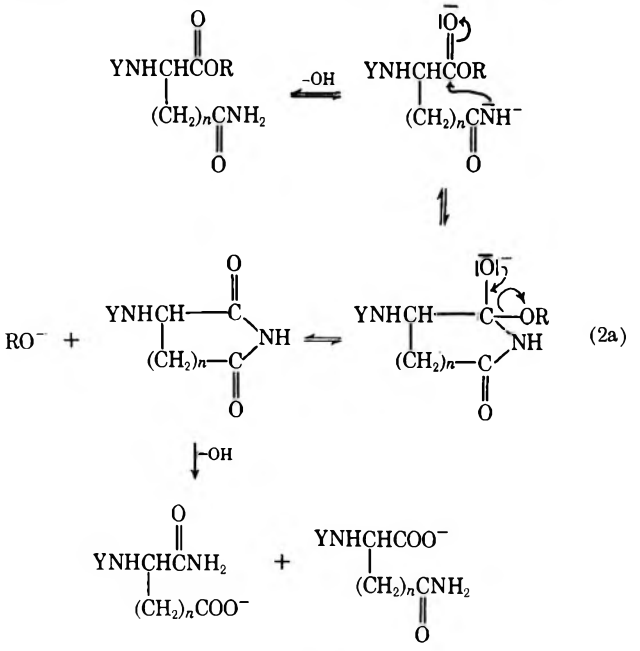
The properties of 2,4-dimethoxybenzyl (Dmb) as a protecting group for the amide side chain of glutamine and asparagine during peptide synthesis are described. 2,4-Dimethoxybenzylamine was prepared by the reduction of 2,4-dimethoxybenzyaldoxime with sodium bis(2-methoxyethoxy)aluminum hydride. The Dmb derivatives obtained by reaction of 2,4-dimethoxybenzylamine and either *N,N'*-dicyclohexylcarbodiimide or *N*-diethylamino-1-propyne with the appropriate amine acid derivatives are crystalline and the Dmb group can be removed by trifluoroacetic acid or anhydrous hydrogen fluoride to give the free amide. No formation of pyroglutamyl peptides or of other side reactions was detected with Dmb-protected glutamyl derivatives, even during saponification. On the contrary, use of alkali with either 2,4-dimethoxybenzyl- or bis(2,4-dimethoxybenzyl)-protected asparaginyl peptides resulted in a mixture of products and is not recommended.

The amide groups of asparagine and glutamine undergo the following side reactions (eq 1–3) during peptide synthesis: (1) dehydration to the corresponding

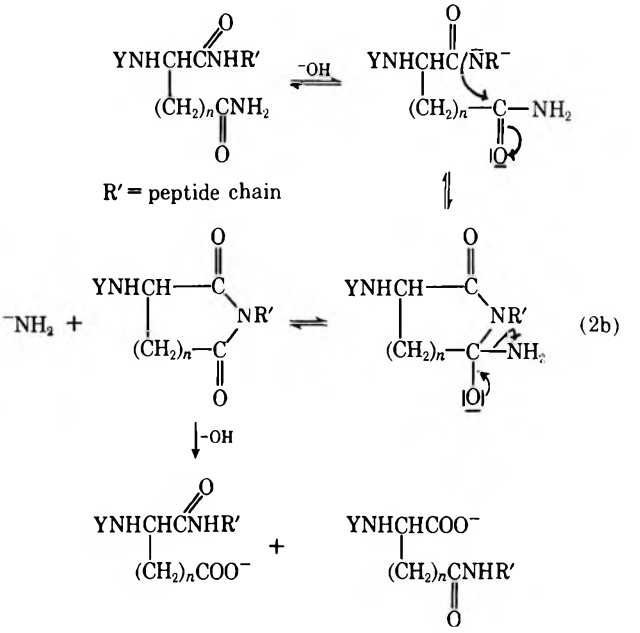


(1)

cyano derivatives;[2-6] (2) formation of imides and subsequent hydrolysis[7-10] [N-protected asparagine or glutamine esters (a), asparaginyl or glutaminyl peptides (b). In this case, the loss of a proton by the action of alkali occurs in both position α and ω. The α site is more reactive because of the greater electrophilic strength of the α carbon atom as compared with that of the ω carbon atom. The subsequent release of the NH_2 group leads to formation of α and ω isomeric peptides, though the latter is obtained in greater amount. Reaction at the ω site causes cleavage of the peptide



(2a)



(2b)

(1) To whom any correspondence should be sent.

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(5) D. V. Kashelikar and C. Ressler, *J. Amer. Chem. Soc.*, **86**, 2467 (1964).

(6) R. Paul and A. S. Kende, *ibid.*, **86**, 4162 (1964).

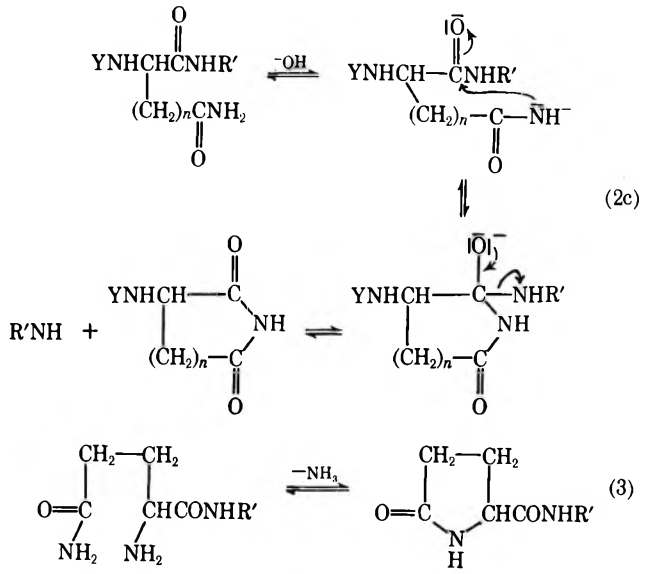
(7) E. Sondheimer and R. W. Holley, *ibid.*, **76**, 2467 (1954).

(8) (a) A. R. Battersby and J. C. Robinson, *J. Chem. Soc.*, 259 (1955); (b) A. R. Battersby and J. C. Robinson, *ibid.*, 2076 (1956).

(9) (a) B. Riniker and R. Schwyzer, *Helv. Chim. Acta*, **44**, 685 (1961); (b) B. Riniker, H. Brunner, and R. Schwyzer, *Angew. Chem.*, **74**, 469 (1962); (c) B. Riniker and R. Schwyzer, *Helv. Chim. Acta*, **47**, 2357 (1964).

(10) G. R. Marshall and R. B. Merrifield, *Biochemistry*, **4**, 2394 (1965).

(c)]; and (3) formation of pyroglutamyl derivatives from glutaminyl peptides.[11,12]



Weygand and his colleagues[13,14] have introduced the protecting group bis(2,4-dimethoxybenzyl), $(Dmb)_2$, in order to prevent the previously mentioned side reactions. The preparation of $(Dmb)_2NH$ is laborious and the $(Dmb)_2$-protected derivatives are usually amorphous; therefore, their characterization is difficult. The possibility of using just one 2,4-dimethoxybenzyl group has been further investigated. 2,4-Dimethoxybenzylamine has been synthesized by a new and easier method, *i.e.*, reduction with sodium bis(2-methoxyethoxy)aluminum hydride of the 2,4-dimethoxybenzaldoxide. The Dmb derivatives are crystalline products which can be easily obtained by reacting 2,4-dimethoxybenzylamine with the corresponding esters of *N*-benzyloxycarbonyl or *N*-*tert*-butyloxycarbonylaspartic and glutamic acids, *via* *N*-diethylamino-1-propyne or *N*,*N*'-dicyclohexylcarbodiimide.[15]

On removal of the ester group or the amino-protective group, the carboxyl or amino components are obtained, respectively. The synthesis of the Dmb-protected asparaginyl or glutaminyl peptides has been carried out from these compounds. The Dmb group was removed using trifluoroacetic acid or anhydrous hydrofluoric acid.

With regard to the action of base, it has been found that Dmb-protected glutaminyl derivatives are stable. In fact, alkaline hydrolysis of *N*-benzyloxycarbonyl-N^{γ}-(2,4-dimethoxybenzyl)-L-glutamine methyl ester, *N*-benzyloxycarbonyl-N^{γ}-(2,4-dimethoxybenzyl)-L-glutaminyl-L-alanine methyl ester, and *N*-*tert*-butyloxycarbonyl-N^{γ}-(2,4-dimethoxybenzyl)-L-glutaminyl-L-alanine methyl ester gave the corresponding free acids in high yield.

On the contrary, alkaline hydrolysis of *N*-benzyloxycarbonyl-N^{β}-(2,4-dimethoxybenzyl)-L-asparaginyl-L-alanine methyl ester and *N*-benzyloxycarbonyl-N^{β}-(2,4-dimethoxybenzyl)-L-asparaginyl-L-alanyl-L-leucyl-L-alanine methyl ester resulted in a mixture of products, according to the side reactions described in 2b. In the case of *N*-benzyloxycarbonyl-N^{β}-(2,4-dimethoxybenzyl)-L-asparagine methyl ester, however, the desired product is easily obtained from the mixture by crystallization.

Even the $(Dmb)_2$ protective group, which makes reaction at the ω site impossible, is not able to prevent the more preferred reaction at the α site, however, in contrast to previously reported observations.[13] In fact, alkaline hydrolysis with 3 equiv of 1 *N* NaOH of *N*-benzyloxycarbonyl-N^{β}-bis(2,4-dimethoxybenzyl)-L-asparaginyl-L-leucine methyl ester[13] and *N*-benzyloxycarbonyl-N^{β}-bis(2,4-dimethoxybenzyl)-L-asparaginyl-L-alanyl-L-leucyl-L-alanine methyl ester yielded, as ascertained by thin layer chromatography, three different products. Therefore, use of alkali with asparaginyl peptides protected either by Dmb or $(Dmb)_2$ is not recommended. No formation of pyroglutamyl derivatives was observed with Dmb-protected carboxamide groups. Thus, on the reaction of the dipeptide ester, prepared by hydrogenolysis of *N*-benzyloxycarbonyl-N^{γ}-(2,4-dimethoxybenzyl)-L-glutaminyl-L-alanine methyl ester in 80% acetic acid, with *N*-*tert*-butyloxycarbonyl-L-alanine *p*-nitrophenyl ester, the tripeptide *N*-*tert*-butyloxycarbonyl-L-alanyl-N^{γ}-(2,4-dimethoxybenzyl)-L-glutaminyl-L-alanine methyl ester was obtained in high yield. In addition, formation of pyroglutamyl derivatives was not observed during removal of the protective groups of *N*-*tert*-butyloxycarbonyl-N^{γ}-(2,4-dimethoxybenzyl)-L-glutamine, *N*-*tert*-butyloxycarbonyl-N^{γ}-(2,4-dimethoxybenzyl)-L-glutaminyl-L-alanine, and *N*-*tert*-butyloxycarbonyl-N^{γ}-(2,4-dimethoxybenzyl)-L-glutaminyl-L-alanyl-L-valyl-L-valine *tert*-butyl ester with trifluoroacetic acid.

Experimental Section

Ascending thin layer chromatograms were run on silica gel G with butan-1-ol–acetic acid–water (4:1:1 v/v) (R_{FA}), butan-1-ol–acetic acid–water–pyridine (15:10:2:3) (R_{FB}), and benzene–ethyl acetate–acetic acid–water (10:10:2:1) (R_{FC}). Descending chromatograms were run on Whatman No. 3 MM paper with butan-1-ol–acetic acid–water (4:1:1) (R_{FD}) or liquified phenol saturated with water and in the presence of a beaker of 0.3% NH_4OH in the tank during each run (R_{FE}). Spots were revealed with ninhydrin solution, and sodium hypochlorite followed by potassium iodide (1%)–starch (1%).[16] Acid hydrolysates of peptides were prepared using 6 *N* hydrochloric acid (110°, 16 hr) and the amino acid composition was determined with a Technicon Auto-Analyzer. Optical rotation were determined with a Perkin-Elmer polarimeter, Model 141. Organic extracts were dried with anhydrous sodium sulfate and evaporations were carried out under reduced pressure in a rotary evaporator. Melting points (uncorrected) were determined in capillary tubes in a Tottoli melting point apparatus (manufactured by W. Büchi).

2,4-Dimethoxybenzaldoxime.—2,4-Dimethoxybenzaldehyde (16.6 g, 0.1 mol) and hydroxylamine hydrochloride (6.9 g, 0.1 mol) in 12% sodium hydroxide (50 ml) and ethanol (12 ml) were gently refluxed for 10 min. After cooling overnight at 0°, the precipitate was filtered and crystallized from ethanol–water, yielding the product (14.8 g, 82%), mp 104–105°.

Anal. Calcd for $C_9H_{11}NO_3$: C, 59.64; H, 6.12; N, 7.73. Found: C, 59.61; H, 6.12; N, 7.77.

(11) D. Theodoropoulos and I. Souchleris, *Acta Chim. Acad. Sci. Hung.*, **44**, 183 (1965).

(12) E. Schnabel, H. Klostermeyer, J. Dahlmaus, and H. Zahn, *Justus Liebigs Ann. Chem.*, **707**, 227 (1967).

(13) (a) F. Weygand, W. Steglich, J. Bjarnason, R. Aktar, and N. Chytil, *Chem. Ber.*, **101**, 3623 (1968); (b) F. Weygand, W. Steglich, and J. Bjarnason, *ibid.*, **101**, 3642 (1968).

(14) P. G. Pietta, F. Chillemi, and A. Corbellini, *ibid.*, **101**, 3649 (1968).

(15) Attempts to prepare these intermediates directly from the symmetrical anhydrides and 2,4-dimethoxybenzylamine were not successful because of the difficulties in separating the mixture of the α and ω amide derivatives which resulted.

(16) H. N. Rydon and P. Smith, *Nature*, **169**, 922 (1952).

2,4-Dimethoxybenzylamine (Dmb-NH$_2$).—A solution of 2,4-dimethoxybenzaldoxime (13.6 g, 75 mmol) in benzene (100 ml) was added under stirring to a solution of sodium bis(2-methoxyethoxy)aluminum hydride (60 g, 0.3 mol) in benzene (45 ml). The mixture was boiled for 1 hr, cooled, and decomposed with 20% sulfuric acid at 0°. After washing with ether, the solution was made alkaline with 10% sodium hydroxide, filtered, and extracted with ether. The ether extracts were dried, concentrated, and treated with HCl–ether. The salt which precipitated was filtered and crystallized from ethanol–ether to give the product hydrochloride (13 g, 86%), mp 185–186°.[13]

A. N^β-(2,4-Dimethoxybenzyl)-L-asparagine Derivatives and Peptides. ***N*-Benzyloxycarbonyl-N^β-(2,4-dimethoxybenzyl)-L-asparagine α-Methyl Ester [Z-Asn(Dmb)-OMe].**—Freshly distilled 1-diethylamino-1-propyne[17,18] (2.6 g, 23.5 mmol) in methylene chloride (25 ml) was added dropwise at 5–10° during 30 min to a stirred solution of α-methyl-*N*-benzyloxycarbonyl-L-aspartic acid (6.6 g, 23.5 mmol) and 2,4-dimethoxybenzylamine (3.92 g, 23.5 mmol) in methylene chloride (100 ml). Stirring was continued at 20–25° for 30 min and then the mixture was evaporated. Crystallization of the residue from ethyl acetate gave the product (7.4 g, 74%): mp 162–163°; R_{FA} 0.80, R_{FC} 0.86; $[\alpha]^{27}D$ +60.1° (*c* 1.03, dimethylformamide).

Anal. Calcd for $C_{22}H_{26}N_2O_7$: C, 61.38; H, 6.08; N, 6.50. Found: C, 61.37; H, 5.94; N, 6.50.

***N*-*tert*-Butyloxycarbonyl-N^β-(2,4-dimethoxybenzyl)-L-asparagine α-Benzyl Ester [Boc-Asn(Dmb)-OBzl].**—This product (mp 102–103°), which crystallized from ethyl acetate–petroleum ether (bp 60–80°), was obtained similarly in 38% yield: R_{FA} 0.62, R_{FC} 0.70; $[\alpha]^{25}D$ −6.4° (*c* 1.0, methanol).

Anal. Calcd for $C_{25}H_{32}N_2O_7$: C, 63.54; H, 6.83; N, 5.93. Found: C, 63.30; H, 6.94; N, 6.06.

***N*-*tert*-Butyloxycarbonyl-N^β-(2,4-dimethoxybenzyl)-L-isoasparagine β-Benzyl Ester [Boc-Asp(Bzl)-NH-Dmb].**—This product (mp 99–100°), which crystallized from ethyl acetate–petroleum ether, was obtained similarly in 78% yield: R_{FA} 0.9, R_{FA} 0.86; $[\alpha]^{25}D$ −10.4° (*c* 1.0, methanol).

Anal. Calcd for $C_{25}H_{32}N_2O_7$: C, 63.54; H, 6.83; N, 5.93. Found: C, 63.20; H, 6.83; N, 6.01.

***N*-Benzyloxycarbonyl-N^β-(2,4-dimethoxybenzyl)-L-asparagine [Z-Asn(Dmb)-OH].**—*N*-Benzyloxycarbonyl-N^β-(2,4-dimethoxybenzyl)-L-asparagine α-methyl ester (4.3 g, 10 mmol) in dioxane (50 ml) and 1 *N* NaOH (11 mmol) were kept at 23–25° for 90 min. After evaporation, the resulting residue was dissolved in water, and the solution was acidified with 1 *N* HCl and then extracted with ethyl acetate. The extracts were washed with water, dried, and evaporated. Crystallization from ethyl acetate gave the product (3.4 g, 81%): mp 152–154°; R_{FA} 0.88, R_{FC} 0.77; $[\alpha]^{27}D$ +3.2° (c 1.0, methanol).

Anal. Calcd for $C_{21}H_{24}N_2O_7$: C, 60.56; H, 5.80; N, 6.72. Found: C, 60.34; H, 5.70; N, 6.71.

The dicyclohexylammonium salt had mp 161–162°.

Anal. Calcd for $C_{33}H_{47}N_3O_7$: C, 66.31; H, 7.92; N, 7.03. Found: C, 66.45; H, 7.70; N, 7.05.

***N*-*tert*-Butyloxycarbonyl-N^β-(2,4-dimethoxybenzyl)-L-asparagine Dicyclohexylammonium Salt [Boc-Asn(Dmb)·DCHA].**—*N*-*tert*-Butyloxycarbonyl-N^β-(2,4-dimethoxybenzyl)-L-asparagine α-benzyl ester (0.94 g, 2 mmol) was hydrogenated in ethanol (15 ml) over 10% palladium on charcoal (0.2 g) for 10 hr. The catalyst was then filtered off and the solution was concentrated. Addition of dicyclohexylamine (0.36 g, 2 mmol) in ether (5 ml) precipitated the corresponding salt, which was filtered and crystallized from ethyl acetate, yielding the product (0.77 g, 68%), mp 124–125°, R_{FC} 0.80.

Anal. Calcd for $C_{30}H_{49}N_3O_7$: C, 63.93; H, 8.50; N, 7.45. Found: C, 63.98; H, 8.47; N, 7.51.

***N*-*tert*-Butyloxycarbonyl-N^α-(2,4-dimethoxybenzyl)-L-isoasparagine Dicyclohexylammonium Salt [Boc-Asp(·DCHA)-NH-Dmb].**—This compound (mp 166–167°, R_{FB} 0.70, R_{FC} 0.75) was prepared similarly in 85% yield.

Anal. Calcd for $C_{30}H_{49}N_3O_7$: C, 63.93; H, 8.50; N, 7.45. Found: C, 64.02; H, 8.45; N, 7.58.

***N*-Benzyloxycarbonyl-N^β-(2,4-dimethoxybenzyl)-L-asparagine *p*-Nitrophenyl Ester [Z-Asn(Dmb)-ONp].**—*N*,*N*′-Dicyclohexylcarbodiimide (1.7 g, 8.2 mmol) was added at 0° to a stirred solution of *N*-benzyloxycarbonyl-N^β-(2,4-dimethoxybenzyl)-L-asparagine (3.4 g, 8.2 mmol) and *p*-nitrophenol (1.36 g, 10 mmol) in dimethylformamide (40 ml). The mixture was kept at 0° for 3 hr and then filtered. After evaporation under reduced pressure, the residue was crystallized from ethanol, yielding the product (3.1 g, 70%), mp 148–149°, R_{FC} 0.9.

Anal. Calcd for $C_{27}H_{27}N_3O_9$: C, 60.33; H, 5.06; N, 7.81. Found: C, 60.31; H, 5.06; N, 7.86.

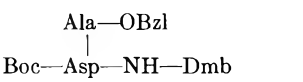
***N*-Benzyloxycarbonyl-N^β-(2,4-dimethoxybenzyl)-L-asparaginyl-L-alanine Methyl Ester [Z-Asn(Dmb)-Ala-OMe].**—*N*-Benzyloxycarbonyl-N^β-(2,4-dimethoxybenzyl)-L-asparagine *p*-nitrophenyl ester (5.90 g, 11 mmol) was added to a solution of L-alanine methyl ester hydrochloride (1.39 g, 10 mmol) and triethylamine (1.4 ml, 10 mmol) in pyridine (40 ml). The mixture was kept overnight at room temperature and then the solvent was removed under reduced pressure. The residue was washed with ether and crystallized from methanol–ethyl acetate. The product had mp 181–182° (3.7 g, 74%), R_{FA} 0.77, R_{FC} 0.70.

Anal. Calcd for $C_{25}H_{31}N_3O_8$: C, 59.88; H, 6.23; N, 8.38. Found: C, 59.77; H, 6.18; N, 8.23.

***N*-Benzyloxycarbonyl-N^β-(2,4-dimethoxybenzyl)-L-asparaginyl-L-alanyl-L-leucyl-L-alanine Methyl Ester [Z-Asn(Dmb)-Ala-Leu-Ala-OMe].**—This compound was prepared similarly in 70% yield starting from *N*-benzyloxycarbonyl-N^β-(2,4-dimethoxybenzyl)-L-asparagine *p*-nitrophenyl ester and L-alanyl-L-leucyl-L-alanine methyl ester (obtained by hydrogenolysis of *N*-benzyloxycarbonyl-L-alanyl-L-leucyl-L-alanine methyl ester): mp 235–236° (from methanol); R_{FA} 0.82, R_{FC} 0.65; $[\alpha]^{27}D$ −9.4° (*c* 1.0, dimethylformamide); amino acid ratios, Asp 1.00, Ala 1.94, Leu 1.02.

Anal. Calcd for $C_{34}H_{47}N_5O_{10}$: C, 59.55; H, 6.90; N, 10.21. Found: C, 59.47; H, 6.90; N, 10.29.

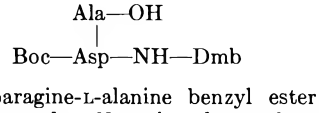
***N*-*tert*-Butyloxycarbonyl-N^α-(2,4-dimethoxybenzyl)-L-isoasparaginyl-L-alanine Benzyl Ester.**—*N*-*tert*-Butyloxycarbonyl-N^α-



(2,4-dimethoxybenzyl)-L-isoasparagine dicyclohexylammonium salt (0.85 g, 1.5 mmol) and L-alanine benzyl ester hydrochloride (0.33 g, 1.5 mmol) were dissolved in methylene chloride (20 ml). After 15-min stirring, *N*,*N*′-dicyclohexylcarbodiimide (0.315 g, 1.5 mmol) was added at 0°, and the mixture was kept at 0° for 12 hr and then filtered. After evaporation under reduced pressure, the residue was crystallized from ethyl acetate, yielding the product (0.57 g, 70%): mp 140–141°; R_{FA} 0.80, R_{FC} 0.70; $[\alpha]^{27}D$ −15.8° (*c* 1.0, dimethylformamide).

Anal. Calcd for $C_{28}H_{37}N_3O_8$: C, 61.86; H, 6.86; N, 7.73. Found: C, 61.86; H, 6.78; N, 7.76.

***N*-*tert*-Butyloxycarbonyl-N^α-(2,4-dimethoxybenzyl)-L-isoasparaginyl-L-alanine.**—*N*-*tert*-Butyloxycarbonyl-N^α-(2,4-dimeth-



oxybenzyl)-L-isoasparagine-L-alanine benzyl ester was hydrogenated similarly to the *N*-*tert*-butyloxycarbonyl-N^β-(2,4-dimethoxybenzyl)-L-asparagine benzyl ester in 88% yield, mp 194–195° crystallized from ethanol–ether, R_{FA} 0.70, R_{FC} 0.64.

Anal. Calcd for $C_{21}H_{31}N_3O_8$: C, 55.63; H, 6.89; N, 9.26. Found: C, 55.49; H, 6.87; N, 9.29.

***N^β*-(2,4-Dimethoxybenzyl)-L-asparagine [H-Asn(Dmb)-OH].**—*N*-Benzyloxycarbonyl-N^β-(2,4-dimethoxybenzyl)-L-asparagine (0.83 g, 2 mmol) in acetic acid (20 ml) was hydrogenated over 10% palladium on charcoal (0.25 g) for 3 hr. The catalyst was filtered off and the solution was evaporated. Crystallization from methanol gave the product (0.64 g, 82%), mp 230–231°, R_{FA} 0.61, R_{FB} 9.72.

Anal. Calcd for $C_{13}H_{18}N_2O_5$: C, 55.31; H, 6.43; N, 9.92. Found: C, 55.50; H, 6.07; N, 9.94.

***N^α*-(2,4-Dimethoxybenzyl)-L-isoasparagine (H-Asp-NH-Dmb).**—*N*-*tert*-Butyloxycarbonyl-N^α-(2,4-dimethoxybenzyl)-L-isoasparagine dicyclohexylammonium salt (0.84 g, 1.5 mmol) was treated with 1 *N* HCl–acetic acid (10 ml) for 30 min. After evaporation, the residue was crystallized from ethanol–ether, yielding the product (0.28 g, 69%), mp 160–162°, R_{FA} 0.65, R_{FB} 0.76.

Anal. Calcd for $C_{13}H_{18}N_2O_5$: C, 55.31; H, 6.43; N, 9.92. Found: C, 55.48; H, 6.09; N, 9.92.

B. *N*-(2,4-Dimethoxybenzyl)-L-glutamine Derivatives and Peptides. ***N*-Benzyloxycarbonyl-N^γ-(2,4-dimethoxybenzyl)-L-**

(17) H. G. Viehe, *Angew. Chem.*, **76**, 571 (1964).

(18) A. S. vanMourik, E. Harryvan, and J. F. Arens, *Recl. Trav. Chim. Pays-Bas*, **84**, 1344 (1965).

glutamine α-Methyl Ester [Z-Gln(Dmb)-OMe].—Freshly distilled 1-diethylamino-1-propyne[17] (2.2 g, 20 mmol) in 20 ml of methylene chloride was added dropwise at 5–10°, during 30 min to a stirred solution of α-methyl-*N*-benzyloxycarbonyl-L-glutamate (5.9 g, 20 mmol) and 2,4-dimethoxybenzylamine (3.34 g, 20 mmol) in 80 ml of methylene chloride. The mixture was kept under stirring at 20–25° for 30 min; then the solvent was evaporated and the residue was extracted with ethyl acetate. The extracts were washed with aqueous sodium bicarbonate, 10% aqueous citric acid, and water, then dried and evaporated. Crystallization of the residue from ethyl acetate–petroleum ether (bp 60–80°) gave the product (6.2 g, 70%): mp 125°; R_{FA} 0.79, R_{FC} 0.7; $[\alpha]^{27}D$ −11.9° (*c* 1.0, methanol).

Anal. Calcd for $C_{23}H_{28}N_2O_7$: C, 62.15; H, 6.35; N, 6.30. Found: C, 61.95; H, 6.45; N, 6.23.

α-Benzyl-*N*-*tert*-butyloxycarbonyl-L-glutamate Dicyclohexylammonium Salt [Boc-Glu(·DCHA)-OBzl].—Freshly distilled 1-diethylamino-1-propyne[17] (3.78 g, 34 mmol) in 20 ml of anhydrous tetrahydrofuran was added dropwise at 5–10° over 30 min to a stirred solution of *N*-*tert*-butyloxycarbonyl-L-glutamic acid (8.4 g, 34.5 mmol) in anhydrous tetrahydrofuran (20 ml). Stirring was continued for 15 min and then benzyl alcohol (10.8 g, 100 mmol) was added; the mixture was treated dropwise with dicyclohexylamine (6.24 g, 34.5 mmol) in ether (100 ml) and was kept at room temperature overnight. The solid precipitate was collected, washed with ether, and crystallized from ethanol, yielding α-benzyl-*N*-*tert*-butyloxycarbonyl-L-glutamate dicyclohexylammonium salt (10.35 g, 58%), mp 174–175° (lit.[19] mp 172°), R_{FA} 0.80, R_{FC} 0.65.

***N*-*tert*-Butyloxycarbonyl-*N*$^{\gamma}$-(2,4-dimethoxybenzyl)-L-glutamine α-Benzyl Ester [Boc-Gln(Dmb)-OBzl].**—α-Benzyl-*N*-*tert*-butyloxycarbonyl-L-glutamate (obtained as an oil by acidification of the salt) (9.9 g, 29.4 mmol) and 2,4-dimethoxybenzylamine (4.9 g, 29.4 mmol) in methylene chloride (250 ml) were treated with *N*,*N*′-dicyclohexylcarbodiimide (6.2 g, 30 mmol) at 0°. The mixture was stirred at 0° for 3 hr and then at room temperature for 2 hr. After filtration and evaporation, the resulting residue was dissolved in ethyl acetate, and the solution was washed with aqueous sodium bicarbonate, 10% aqueous citric acid, and water, then dried and evaporated. Crystallization of the residue from ethyl acetate–petroleum ether (bp 30–60°) yielded *N*-*tert*-butyloxycarbonyl-*N*$^{\gamma}$-(2,4-dimethoxybenzyl)-L-glutamine α-benzyl ester (10 g, 70%): mp 111–112°; R_{FA} 0.90, R_{FC} 0.87; $[\alpha]^{25}D$ −6.5° (*c* 1.0, methanol).

Anal. Calcd for $C_{26}H_{34}N_2O_7$: C, 64.18; H, 7.04; N, 5.75. Found: C, 64.33; H, 7.12; N, 5.78.

***N*-Benzyloxycarbonyl-*N*$^{\gamma}$-(2,4-dimethoxybenzyl)-L-glutamine [Z-Gln(Dmb)-OH].**—Sodium hydroxide hydrate (0.64 g, 16 mmol) in water (16 ml) was added dropwise over 10 min at 20–25° to a stirred solution of *N*-benzyloxycarbonyl-*N*$^{\gamma}$-(2,4-dimethoxybenzyl)-L-glutamine α-methyl ester (6.2 g, 14 mmol) in dioxane (90 ml). The mixture was stirred at 20–25° for 60 min and then, after removal of the dioxane, acidified to pH 3 with 1 *N* HCl and extracted with ethyl acetate. The extracts were washed with water, dried, and evaporated, and the residue was treated with dicyclohexylamine (2.54 g, 14 mmol) in ethyl acetate (35 ml), giving the salt (7.5 g, 88%), mp 110°, $[\alpha]^{25}D$ +5.5° (*c* 1.0, dimethylformamide).

Anal. Calcd for $C_{34}H_{49}N_3O_7$: C, 66.75; H, 7.97; N, 6.86. Found: C, 66.74; H, 8.07; N, 6.86.

The acid, prepared by acidification of the salt with 0.5 *M* citric acid, was crystallized from ethyl acetate, mp 136–137°, R_{FA} 0.85, R_{FC} 0.48.

***N*-*tert*-Butyloxycarbonyl-*N*$^{\gamma}$-(2,4-dimethoxybenzyl)-L-glutamine [Boc-Gln(Dmb)-OH].**—*N*-*tert*-Butyloxycarbonyl-*N*$^{\gamma}$-(2,4-dimethoxybenzyl)-L-glutamine α-benzyl ester (6.5 g, 13.4 mmol) in ethanol (100 ml) was hydrogenated at room temperature and pressure over 10% palladium on charcoal (1.2 g) for 8 hr. After removal of the catalyst, the solution was evaporated and the residue was dissolved in ethyl acetate. The solution was extracted with aqueous sodium bicarbonate. The extracts were acidified with HCl and extracted with ethyl acetate. The extracts were dried and evaporated and the resulting residue was crystallized from ethyl acetate–petroleum ether, yielding the product (4.65 g, 88%), mp 110–111°, R_{FA} 0.75, R_{FC} 0.68.

Anal. Calcd for $C_{19}H_{28}N_2O_7$: C, 57.56; H, 7.12; N, 7.07. Found: C, 57.43; H, 7.22; N, 7.18.

(19) E. Schröder and E. Klieger, *Justus Liebigs Ann. Chem.*, **673**, 196 (1964).

***N*-Benzyloxycarbonyl-*N*$^{\gamma}$-(2,4-dimethoxybenzyl)-L-glutamine *p*-Nitrophenyl Ester [Z-Gln(Dmb)-ONp].**—This compound was prepared similarly to the asparagine analog in 72% yield: mp 149–150° (from ethanol); R_{FC} 0.90; $[\alpha]^{25}D$ −16.0° (*c* 1.0, methanol).

Anal. Calcd for $C_{28}H_{29}N_3O_9$: C, 60.97; H, 5.30; N, 7.62. Found: C, 60.88; H, 5.43; N, 7.52.

***N*-*tert*-Butyloxycarbonyl-*N*$^{\gamma}$-(2,4-dimethoxybenzyl)-L-glutamine *p*-Nitrophenyl Ester [Boc-Gln(Dmb)-ONp].**—This compound was prepared similarly in 90% yield: mp 134–135°; R_{FC} 0.90; $[\alpha]^{25}D$ −18.1° (*c* 1.0, methanol).

Anal. Calcd for $C_{25}H_{31}N_3O_9$: C, 58.01; H, 6.04; N, 8.12. Found: C, 57.86; H, 6.31; N, 8.24.

***N*-Benzyloxycarbonyl-*N*$^{\gamma}$-(2,4-dimethoxybenzyl)-L-glutaminyl-L-alanine Methyl Ester [Z-Gln(Dmb)-Ala-OMe].**—This was prepared similarly to the asparagine analog in 70% yield: mp 179–180° (from ethyl acetate), R_{FA} 0.75, R_{FC} 0.65; $[\alpha]^{25}D$ −6.3° (*c* 1.0, dimethylformamide).

Anal. Calcd for $C_{26}H_{33}N_3O_8$: C, 60.57; H, 6.45; N, 8.15. Found: C, 60.47; H, 6.47; N, 8.16.

***N*-*tert*-Butyloxycarbonyl-*N*$^{\gamma}$-(2,4-dimethoxybenzyl)-L-glutaminyl-L-alanine Methyl Ester [Boc-Gln(Dmb)-Ala-OMe].**—This peptide was prepared similarly in 86% yield: mp 133–134° (from ethyl acetate–petroleum ether); R_{FA} 0.82, R_{FC} 0.71; $[\alpha]^{25}D$ 7.0° (*c* 1.0, dimethylformamide).

Anal. Calcd for $C_{23}H_{35}N_3O_8$: C, 57.37; H, 7.33; N, 8.73. Found: C, 57.37; H, 7.35; N, 8.57.

***N*-Benzyloxycarbonyl-*N*$^{\gamma}$-(2,4-dimethoxybenzyl)-L-glutaminyl-L-alanine [Z-Gln(Dmb)-Ala-OH].**—*N*-Benzyloxycarbonyl-*N*$^{\gamma}$-(2,4-dimethoxybenzyl)-L-glutaminyl-L-alanine methyl ester (1.0 g, 2 mmol) in dioxane (30 ml) and 0.5 *N* NaOH (5 mmol) were kept at 23–25° for 90 min. The mixture was acidified with 1 *N* HCl, evaporated, and then extracted with ethyl acetate. The extracts were washed with water, dried, and evaporated. Crystallization from ethyl acetate gave the product (0.80 g, 80%): mp 193–194°; R_{FA} 0.71, R_{FC} 0.55; $[\alpha]^{25}D$ −1.9° (*c* 1.0, dimethylformamide).

Anal. Calcd for $C_{25}H_{31}N_3O_8$: C, 59.87; H, 6.23; N, 8.38. Found: C, 59.51; H, 6.29; N, 8.30.

***N*-*tert*-Butyloxycarbonyl-*N*$^{\gamma}$-(2,4-dimethoxybenzyl)-L-glutaminyl-L-alanine [Boc-Gln(Dmb)-Ala-OH].**—This compound was prepared similarly in 93% yield: mp 159–160° (from ethanol–ether); R_{FA} 0.68, R_{FC} 0.54; $[\alpha]^{25}D$ 1.2° (*c* 1.0, dimethylformamide).

Anal. Calcd for $C_{22}H_{33}N_3O_8$: C, 56.52; H, 7.12; N, 8.99. Found: C, 56.87; H, 6.91; N, 8.84.

***N*-*tert*-Butyloxycarbonyl-L-alanyl-*N*$^{\gamma}$-(2,4-dimethoxybenzyl)-L-glutaminyl-L-alanine Methyl Ester [Boc-Ala-Gln(Dmb)-Ala-OMe].**—*N*-Benzyloxycarbonyl-*N*$^{\gamma}$-(2,4-dimethoxybenzyl)-L-glutaminyl-L-alanine methyl ester (0.21 g, 0.41 mmol) in 90% aqueous acetic acid (25 ml) was hydrogenated at room temperature and pressure over 10% palladium on charcoal (0.05 g) for 4–5 hr. After removal of the catalyst, the solution was evaporated and the residue was dissolved in pyridine (20 ml). To this solution *N*-*tert*-butyloxycarbonyl-L-alanine *p*-nitrophenyl ester (0.155 g, 0.5 mmol) was added and the mixture was kept at room temperature for 40 hr. Then the solvent was removed under reduced pressure and the residue was extracted with ethyl acetate. The extracts were washed with aqueous sodium bicarbonate, 10% aqueous citric acid, and water, then dried and evaporated. Crystallization of the residue from ethyl acetate–ether gave the product (0.17 g, 75%), mp 126–127°, R_{FA} 0.64, R_{FC} 0.57.

Anal. Calcd for $C_{26}H_{40}N_4O_9$: C, 56.51; H, 7.28; N, 10.14. Found: C, 56.87; H, 7.23; N, 10.18.

L-Valyl-L-valine *tert*-Butyl Ester (H-Val-Val-OtBu).—*N*,*N*′-Dicyclohexylcarbodiimide (3.7 g, 18 mmol) in methylene chloride (10 ml) was added at 0° to a stirred solution of L-valine *tert*-butyl ester (3.1 g, 18 mmol) and *N*-benzyloxycarbonyl-L-valine (4.5 g, 18 mmol) in methylene chloride (50 ml). The mixture was kept at 20–22° for 20 hr and then filtered. The filtrate was washed with aqueous sodium bicarbonate, 10% aqueous citric acid, and water, then dried and evaporated. The residue in ethanol (60 ml) was hydrogenated at room temperature and pressure over 10% palladium on charcoal (1.5 g) until evolution of CO_2 ceased (5 hr). After removal of the catalyst, the solution was evaporated to give an oil (4.28 g), R_{FA} 0.47, R_{FB} 0.55.

***N*-Benzyloxycarbonyl-L-alanyl-L-valyl-L-valine *tert*-Butyl Ester (Z-Ala-Val-Val-OtBu).**—*N*-Benzyloxycarbonyl-L-alanine *p*-nitrophenyl ester (5.5 g, 16 mmol) was added to a solution of

L-valyl-L-valine *tert*-butyl ester (4.28 g, 15.8 mmol) in pyridine (40 ml). The mixture was kept at room temperature for 40 hr and then the solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate, and the solution was washed with aqueous sodium bicarbonate, 10% aqueous citric acid, and water, then dried and evaporated. Crystallization from ethyl acetate–petroleum ether gave the product (4.47 g, 60%), mp 150–151°, R_{FA} 0.70, R_{FC} 0.87.

Anal. Calcd for $C_{25}H_{39}N_3O_6$: C, 62.87; H, 8.23; N 8.8 0. Found: C, 62.86; H, 8.06; N, 8.58.

N-tert-**Butyloxycarbonyl-N^{γ}-(2,4-dimethoxybenzyl)-L-glutaminyl-L-alanyl-L-valyl-L-valine *tert*-Butyl Ester [Boc-Gln(Dmb)-Ala-Val-Val-OtBu].**—*N-tert*-Butyloxycarbonyl-N^{γ}-(2,4-dimethoxybenzyl)-L-glutamine *p*-nitrophenyl ester (0.7 g, 1.35 mmol) was added to a solution of L-alanyl-L-valyl-L-valine *tert*-butyl ester (0.47 g, 1.35 mmol, obtained by hydrogenolysis of the corresponding *N*-benzyloxycarbonyl derivative) in pyridine (15 ml). The mixture was kept at room temperature for 40 hr and then the solvent was evaporated. After ether trituration, the residue was crystallized from ethyl acetate to give the product (0.65 g, 68%), mp 151–152°, R_{FC} 0.84.

Anal. Calcd for $C_{36}H_{59}N_5O_{10}$: C, 59.89; H, 8.24; N, 9.70. Found: C, 59.83; H, 8.08; N, 9.82.

N^{γ}-(2,4-Dimethoxybenzoyl)-L-glutamine [H-Gln(Dmb)-OH].—This product was prepared similarly to the asparagine analog, mp 240–241° (from methanol), R_{FA} 0.56, R_{FB} 0.64.

Anal. Calcd for $C_{14}H_{20}N_2O_5$: C, 56.75; H, 6.80; N, 9.46. Found: C, 56.77; H, 6.83; N, 9.44.

C. Cleavage of the 2,4-Dimethoxybenzyl Protecting Group. L-Asparagine. a.—*N*-Benzyloxycarbonyl-N^{β}-(2,4-dimethoxybenzyl)-L-asparagine (0.134 g, 0.32 mmol) in 90% aqueous acetic acid (10 ml) was hydrogenated at room temperature and pressure over 10% palladium on charcoal (0.025 g) until evolution of CO_2 ceased. After removal of the catalyst, the solution was evaporated and the residue was dissolved in trifluoroacetic acid (1 ml). The solution was kept at room temperature for 18 hr and then evaporated. The trifluoroacetic salt obtained after ether titration was crystallized from 50% aqueous ethanol (in the presence of a few crystals of sodium acetate) to give L-asparagine (25 mg, 60%): R_{FA} 0.17, R_{FD} 00.8; $[\alpha]^{25}D$ −12° (*c* 2.0, 1 *N* NaOH).

b.—*N*-Benzyloxycarbonyl-N^{β}-(2,4-dimethoxybenzyl)-L-asparagine or *N-tert*-butyloxycarbonyl-N^{β}-(2,4-dimethoxybenzyl)-L-asparagine were added to trifluoroacetic acid (5 ml) and the resulting solution was refluxed for 1 hr. Then the solution was evaporated and the residue was crystallized from 50% ethanol (in the presence of a few crystals of sodium acetate) to give L-asparagine in 75–80% yield.

c.—*N*-Benzyloxycarbonyl-N^{β}-(2,4-dimethoxybenzyl)-L-asparagine or *N-tert*-butyloxycarbonyl-N^{β}-(2,4-dimethoxybenzyl)-L-asparagine were treated with anhydrous hydrofluoric acid[20] for 3 hr. Crystallization of the residue from 50% ethanol (in the presence of a few crystals of sodium acetate) gave L-asparagine in 80% yield.

Isoasparagine.—This compound (R_{FA} 0.27, R_{FD} 0.15) was prepared similarly in 70% yield.

L-Glutamine.—This compound (R_{FA} 0.15, R_{FE} 0.55) was prepared similarly in 70% yield. It appeared identical with an authentic sample of L-glutamine.

(20) J. M. Stewart and J. D. Young, "Solid Phase Peptide Synthesis," W. H. Freeman, San Francisco, Calif., 1969.

L-Glutaminyl-L-alanine (H-Gln-Ala-OH).—This peptide was prepared similarly in 75% yield, mp 174–175° (lit.[21] 174–178°) (from acetic acid–water), R_{FA} 0.41, $[\alpha]D$ +8.30° (c 1.0, 1 *N* hydrochloric acid).

L-Glutaminyl-L-alanyl-L-valyl-L-valine (H-Gln-Ala-Val-Val-OH).—*N-tert*-Butyloxycarbonyl-N^{γ}-(2,4-dimethoxybenzyl)-L-glutaminyl-L-alanyl-L-valyl-L-valine *tert*-butyl ester (0.65 g, 0.9 mmol) was added at 0° to trifluoroacetic acid (10 ml) and the resulting solution was kept at room temperature for 48 hr. Dry ether (50 ml) was added and the peptide trifluoroacetate was collected, dissolved in water (10 ml), and chromatographed on Amberlite IRA-400 in the OH^- form. Crystallization of the residue obtained by evaporation from ethanol yielded the product (30 mg, 80%): R_{FA} 0.45, R_{FB} 0.50; $[\alpha]^{20}D$ −33.88° (*c* 1.0, acetic acid).

Anal. Calcd for $C_{18}H_{32}N_6O_6 \cdot H_2O$: C, 49.88; H, 8.18; N, 16.10. Found: C, 50.0; H, 8.16; N, 16.01.

Registry No.—2,4-Dimethoxybenzaldoxime, 31874-34-7; Dmb-NH_2 HCl, 20781-21-9; Z-Asn(Dmb)-OMe, 31874-64-3; Boc-Asn(Dmb)-OBzl, 31874-36-9; Boc-Asp(Bzl)-NH-Dmb, 31874-37-0; Z-Asn(Dmb)-OH, 31874-38-1; Z-Asn(Dmb)-OH dicyclohexylammonium salt, 31874-39-2; Boc-Asn(Dmb)·DCHA, 32017-42-8; Boc-Asp(·DCHA)-NH-Dmb, 31874-40-5; Z-Asn(Dmb)-ONp, 31874-41-6; Z-Asn(Dmb)-Ala-OMe, 31874-42-7; Z-Asn(Dmb)-Ala-Leu-Ala-OMe, 31874-43-8; H-Asn(Dmb)-OH, 31874-46-1; H-Asp-NH-Dmb, 31874-47-2; Z-Gln(Dmb)-OMe, 31874-48-3; Boc-Glu(·DCHA)-OBzl, 30924-91-5; Boc-Gl(Dmb)-OBzl, 31874-50-7; Z-Gln(Dmb)-OH, 31874-51-8; Boc-Gln(Dmb)-OH, 31874-52-9; Z-Gln(Dmb)-ONp, 31874-53-0; Boc-Gln(Dmb)-ONp, 31874-54-1; Z-Gln(Dmb)-Ala-OMe, 31874-56-3; Boc-Gln(Dmb)-Ala-OMe, 31874-57-4; Z-Gln(Dmb)-Ala-OH, 31874-58-5; Boc-Gln(Dmb)-Ala-OH, 31874-59-6; Boc-Ala-Gln(Dmb)-Ala-OMe, 31874-60-9; H-Val-Val-OtBu, 31874-61-0; Z-Ala-Val-Val-OtBu, 31874-62-1; Boc-Gln(Dmb)-Ala-Val-Val-OtBu, 31874-63-2; H-Gln(Dmb)-OH, 31874-55-2; Z-Gln(Dmb)-OH·DCHA, 31874-65-4; H-Gln-Ala-Val-Val-OH, 31874-66-5; glutamine, 56-85-9; asparagine, 70-47-3; *N-tert*-butyloxycarbonyl-N^{α}-(2,4-dimethoxybenzyl)-L-isoasparaginyl-L-alanine benzyl ester, 31874-44-9; *N-tert*-butyloxycarbonyl-N^{α}-(2,4-dimethoxybenzyl-L-isoasparaginyl-L-alanine, 31874-45-0.

Acknowledgments.—The authors are grateful for support to the National Institutes of Health (AM-13025) and to the American Heart Association for an Established Investigatorship (GRM).

(21) E. Sondheimer and R. W. Holley, *J. Amer. Chem. Soc.*, **76**, 2816 (1954).

Photochemistry of Mercaptoles[1]

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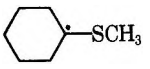
Received April 21, 1971

The photochemistry of 1,1-bis(methylthio)cyclohexane and several cyclic mercaptoles containing a carbon–carbon double bond (**7**, **14**) or an aromatic ring (**19**, **23**, **24**, **28**, **31**, **33**) has been studied. The observed results are compared with the photochemical reactions of simple, cyclic mercaptoles.

Previous investigations of the photochemical reactions of cyclic mercaptoles derived from cyclohexanone and cyclopentanone established two major pathways of reaction.[3] These are indicated in Scheme I for the mercaptoles of cyclohexanone. When $n = 3$, path a was the major pathway and gave predominantly the cis product **1**. When $n = 2$, the predominant reaction was *via* path b to products derived from the thione **2**.

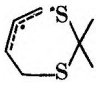
The effects of other changes in the structure of the mercaptole on the reaction course on irradiation in cyclohexane have been investigated. The results are summarized in Table I. Irradiation of the acyclic mercaptole **3** yielded mainly **4** and **6** along with a small amount of **5**. Initial homolytic cleavage of the C–S bond of **3** to structure I and $CH_3S\cdot$ seems obvious, but the



I

poor material balance prevents further conclusions on the pathway. If **5** and CH_3SH are formed from hydrogen atom transfer between the radicals, there is no addition of CH_3SH to **5** to form *cis*-1,2-bis(methylthio)-cyclohexane by an intermolecular pathway analogous to formation of **1**. The hydrogen atom source for converting structure I to **4** is not the solvent since a similar product mixture is obtained from irradiation of **3** in Freon-113 (47% reaction: 17% **4**, 3% **5**, and 11% **6**).

Derivatives of 1,3-dithiacyclohept-5-ene were irradiated to determine whether cleavage of the allylic C–S bond would be the preferred path. Irradiation of **7** gave **8** as the major product. Formation of **8** suggests involvement of the diradical **13**. Products **9**, **10**, and **11** undoubtedly arise from acetone thione which



13

may be formed from **13** or from initial cleavage as previously observed.[3] Product **12** may arise from reaction of **13** or thione with solvent.[3] Photolysis of **14** proceeds in similar fashion except no trithiolane product is observed. If any dihydrothiophene (or thiophene) were formed, its presence would have gone undetected in the removal of the solvent.

The benzo[*e*]-1,3-dithiacyclohept-5-ene analogs **19**, **23**, and **24** were also studied for comparison with **7** and **14**. In all three cases, the major photochemical

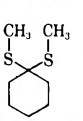
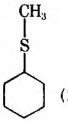
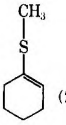
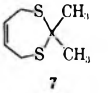
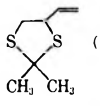
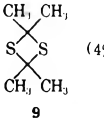
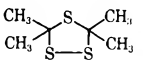
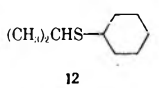
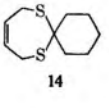
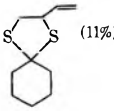
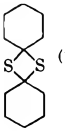
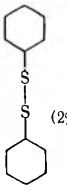
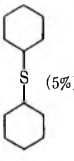
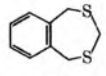
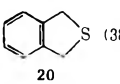
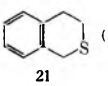
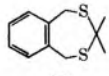
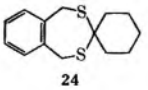
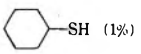
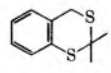
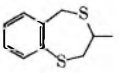
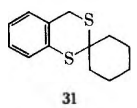
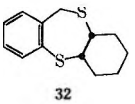
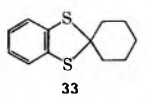
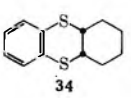
(1) This research has been supported by National Science Foundation Grant No. GP-7831 and by National Institutes of Health Grant No. AI-09300.

(2) National Institutes of Health Predoctoral Fellow, 1966–1968.

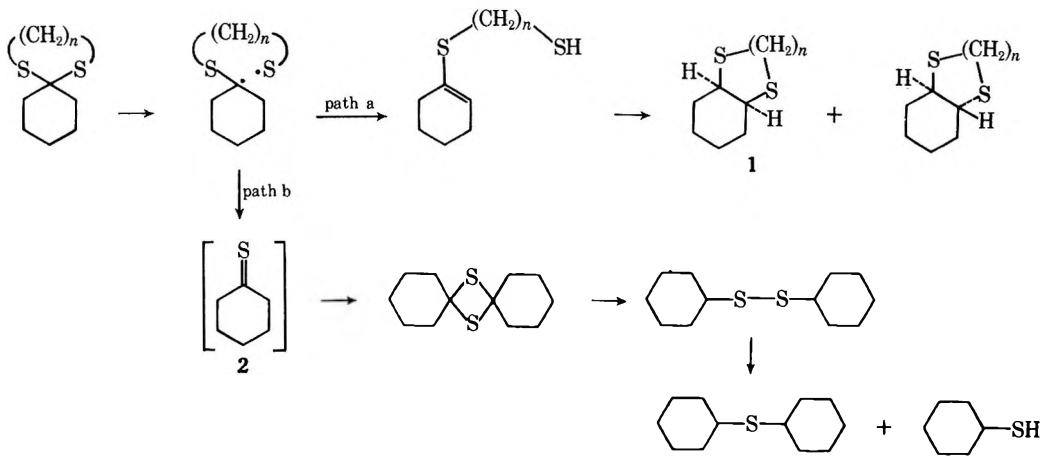
(3) J. D. Willett, J. R. Grunwell, and G. A. Berchtold, *J. Org. Chem.*, **33**, 2297 (1968).

TABLE I

PRODUCTS FROM IRRADIATION OF MERCAPTOLES IN CYCLOHEXANE

Mercaptole	Time, hr	Mercaptole consumed, %	Products (% conversion)
 3	4	65	 4 (27%),  5 (2%), CH_3SSCH_3 6 (18%)
 7	18	89	 8 (25%),  9 (4%), $(CH_3)_2CHSSCH(CH_3)_2$ 10 (3%)
			 11 (8%),  12 (4%)
 14	15	89	 15 (11%),  16 (13%),  17 (2%),  18 (5%)
 19	10	93	 20 (38%),  21 (10%),  22 (2%)
 23	8	85	20 (41%), 9 (14%) 10 (9%), 11 (3%)
 24	12	95	20 (13%), 16 (15%), 17 (6%), 18 (2%),  25 (1%)
 28	41	67	 29 (15%), 9 (4%), 10 (3%)
 31	42	87	 32 (5%), 16 (6%), 17 (6%), 18 (2%)
 33	16	62	 34 (16%)

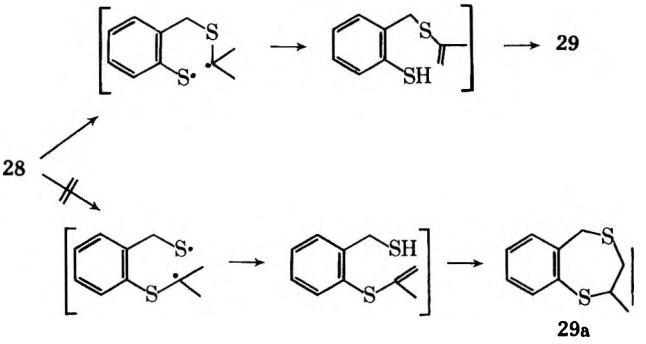
SCHEME I



reaction involves elimination of thione and formation of 2,5-dihydro-3,4-benzothiophene (**20**). All other products, except **21**, are derived from thione as described earlier. The presence of **21** represents a previously unobserved extrusion of sulfur on irradiation of mercaptoles. Whether the reaction occurs through initial homolytic cleavage to form **26** or **27** which eliminates thioformaldehyde and cyclizes to **20** or eliminates sulfur and cyclizes to **21** is open to question.

Photolysis of **28** gave the rearrangement product **29** (analogous to the formation of **1**[3]) in addition to **9** and **10** in low yield. No **29a** was observed. The initial C–S bond cleavage occurs only in the direction to give the more stable thiyl radical as indicated in Scheme II. Irradiation of **31** and **33** produced products from the same photochemical rearrangement. The structure of **29** was established by synthesis of an authentic sample (see Experimental Section).

SCHEME II



Experimental Section[4]

Photochemical Studies.—The photochemical results are listed in Table II. Photolysis solvents were purified by the following procedures. Cyclohexane (Eastman Spectrograde) was distilled under N_2 from BaO through a 2-ft Vigreux column. *tert*-Butyl alcohol (Eastman reagent) was distilled under N_2 from Na through a 2-ft column. Freon-113 (Allied Chemical Co.) was distilled under N_2 from NaH through a 2-ft Vigreux column. In general, the solvents were distilled directly into the photolysis vessel and degassed with prepurified N_2 for 2–3 hr, and the photolysis was carried out under an atmosphere of N_2.

TABLE II

PHOTOCHEMICAL EXPERIMENTS

Compd irradiated (g)	Solvent (ml)	Time, hr	Components of product mixture (% yield)
3 (0.618)	Cyclohexane (75 ml)	4	**3** (35%), **4** (27%), **5** (2%), **6** (18%)
3 (3.385)	Freon-113 (600)	15.5	**3** (53%), **4** (17%), **5** (3%), **6** (11%)
7 (2.427)	Cyclohexane (600)	18	**7** (11%), **8** (25%), **9** (4%), **10** (3%), **11** (8%), **12** (4%)
14 (3.92)	Cyclohexane (600)	15	**14** (11%), **15** (11%), **16** (13%), **17** (2%), **18** (5%)
19 (5.27)	Cyclohexane (600)	10	**19** (7%), **20** (38%), **21** (10%), **22** (2%)
23 (3.42)	Cyclohexane (600)	3	**23** (15%), **9** (14%), **10** (9%), **11** (3%), **20** (41%)
24 (2.85)	Cyclohexane (600)	12	**24** (5%), **16** (15%), **17** (6%), **18** (2%), **20** (13%), **25** (1%)
28 (3.32)	Cyclohexane (600)	41	**28** (67%), **9** (4%), **10** (3%), **29** (15%)
31 (3.80)	Cyclohexane (600)	42	**31** (13%), **16** (6%), **17** (6%), **18** (2%), **32** (5%)
33 (2.21)	Cyclohexane (600)	16	**33** (38%), **34** (16%)

The light source was a Rayonet photochemical reactor, Model RPR 100 (Southern New England Ultraviolet Co.), reactor barrel 10 (diameter) × 15 in. (depth) with 16 lamps (2537 Å) in a circular bank.

Solutions were stirred with a magnetic stirring bar, and quartz vessels were equipped with a water-cooled condenser. Photolyses were monitored by ir or glpc with aliquots withdrawn at convenient intervals of time. Products were characterized by

(4) Infrared spectra were taken on a Perkin-Elmer Model 237 or 337 spectrophotometer. Ultraviolet spectra were taken on a Cary Model 14 spectrophotometer. The nmr spectra were taken on a Varian A-60 or T-60, and chemical shift data are reported in parts per million downfield from tetramethylsilane as an internal standard at 0.00. Mass spectra were run on a Hitachi Perkin-Elmer RMU-6D mass spectrometer with an ionizing potential of 80 eV and are expressed in per cent relative intensity relative to the most intense peak as 100%. Melting points were taken on a Thomas-Hoover "Uni Melt" and are corrected. Gas chromatographic analyses and isolations were carried out on either an F & M Model 810 research gas chromatograph or a Hewlett-Packard Model 5750 gas chromatograph with thermal conductivity detectors using 0.25-in.-diameter columns of the following type: 6 ft, 10% SE-30; 4 ft, 20% SE-30; 4 ft, 10% LAC-446; or 4 ft, 20% Versamid-800 (all on 60–80 mesh Chromosorb P). Microanalyses were performed by Scandinavian Microanalytical Laboratory, Herlev, Denmark, Galbraith Laboratories, Knoxville, Tenn., or Mrs. Nancy Alvord, of this department.

collection from glpc and comparison with authentic samples. Glpc yields are based on the addition of a known amount of hydrocarbon as an internal standard after irradiation.[5]

1,1-Bis(methylthio)cyclohexane (3).—To a solution of cyclohexanone (50.8 g, 0.52 mol) in 250 ml of benzene in a three-necked flask equipped with a Dry Ice condenser and a gas inlet tube was added methyl mercaptan (50 g, 1.04 mol). Hydrogen chloride gas was bubbled through the solution for 2 hr. The solvent was removed under reduced pressure, and the residue was dissolved in ether. The solution was washed with 5% NaOH solution and saturated NaCl solution and dried ($MgSO_4$). The ether was removed under reduced pressure and the residue was distilled to give 70.2 g (77%) of **3**: bp 68–70° (0.4 mm); ir (CCl_4) 2965, 2850, 1445, 1270, 1250, 1180, 1130, 1010, 950, and 865 cm^{-1}; uv max (cyclohexane) 237 nm (ϵ 991); nmr ($CDCl_3$) δ 1.05–1.90 (10 H, m) and 2.02 ppm (6 H, s); mass spectrum *m/e* (rel intensity) 176 (10), 128 (70), 88 (14), 80 (100), 78 (14), 60 (21), 54 (16), 45 (12), 41 (18), and 39 (13).

Anal. Calcd for $C_8H_{16}S_2$: C, 54.48; H, 9.14; S, 36.37. Found: C, 54.66; H, 9.24; S, 36.45.

Cyclohexyl Methyl Sulfide (4).—Sulfide 4 was prepared in 65% yield according to the procedure of Weibull,[6] bp 77–78° (20 mm) [lit.[6] bp 68–68.5° (18 mm)].

Cyclohexenyl Methyl Sulfide (5).—The structure of **5** was assigned on the basis of the following spectral data: ir (CCl_4) 2920, 1647, 1445, 1340, and 1132 cm^{-1}; mass spectrum *m/e* (rel intensity) 128 (54), 113 (22), 100 (15), 85 (38), 81 (100), 80 (54), 79 (50), 77 (17), 71 (13), 67 (11), 61 (11), 59 (13), 53 (32), 51 (15), 45 (29), 41 (43), and 39 (39).

Dimethyl Disulfide (6).—The authentic sample of **6** was purchased from Eastman Organic Chemicals.

2,2-Dimethyl-1,3-dithiacyclohept-5-ene (7).—*cis*-1,4-Dichloro-2-butene[7] was converted to *cis*-2-butene-1,4-dithiol diacetate in 47% yield with thiolacetic acid in pyridine, bp 91–92° (0.08 mm) [lit.[8] bp 81–83° (0.1 mm)]. The dithiol diacetate was converted to *cis*-2-butene-1,4-dithiol in 74% yield with KOH in methanol, bp 55–56° (0.2 mm) [lit.[9] bp 80–81° (11 mm)].

To a solution of 11.6 g (0.2 mol) of acetone in 200 ml of benzene containing 20 mg of *p*-toluenesulfonic acid was added 24.0 g (0.20 mol) of *cis*-2-butene-1,4-dithiol. The mixture was heated under reflux for 18 hr while the water formed was removed by a Dean-Stark trap. The mixture was cooled, washed with 10% NaOH solution and water, and dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue was purified by column chromatography on silicic acid with pentane as eluent. The product was further purified by distillation, repeated fractional recrystallizations from pentane at low temperature (Dry Ice–isopropyl alcohol), and short-path distillation to give 6.82 g (21%) of pure **7**: bp 58–61° (0.4 mm); ir (CCl_4) 3015, 2960, 2910, 2855, 1650, 1438, 1380, 1362, 1162, 1150, and 1112 cm^{-1}; uv max (cyclohexane) 227 nm (ϵ 1840) and 257 (398); nmr (CCl_4) δ 1.68 (6 H, s), 3.2–3.4 (4 H, m) and 5.8–6.0 ppm (2 H, m); mass spectrum *m/e* (rel intensity) 160 (27), 106 (58), 95 (12), 86 (16), 85 (36), 75 (11), 74 (28), 72 (12), 59 (79), 58 (12), 57 (13), 45 (35), 43 (100), 42 (62), and 41 (75).

Anal. Calcd for $C_7H_{12}S_2$: C, 52.44; H, 7.54; S, 40.00. Found: C, 52.70; H, 7.74; S, 39.79.

2,2-Dimethyl-4-vinyl-1,3-dithiacyclopentane (8).—To a solution of 16.8 g (0.100 mol) of 86% KOH in 75 ml of methanol was added 30 g of CS_2, followed by slow addition of 7 g (0.10 mol) of butadiene monoxide (K and K Laboratories). The solution was stirred for 12 hr at room temperature and the excess CS_2 was removed under reduced pressure. Water was added to the residue and the mixture was extracted with ether. The ether layer was washed with water and dried ($MgSO_4$). The solvent was removed under reduced pressure to give 13.3 g (83%) of crude 3-butene-1,2-dithiol trithiocarbonate as a light orange oil. Attempts to induce crystallization were unsuccessful. The product darkened rapidly on exposure to the atmosphere. A small sample was short path distilled: bp 120° (0.7 mm); ir (CCl_4) 1635, 1425, 1075, 975, 930, 808, and 735 cm^{-1}; nmr (CCl_4) δ 3.6–4.1 (3 H, m) and 4.8–6.6 ppm (4 H, m); mass spectrum *m/e* (rel intensity) 162 (35), 108 (14), 86 (58), 85 (100), 71 (11), 64 (15), 54 (15), 53 (19), 45 (41), and 39 (28).

Anal. Calcd for $C_5H_6S_3$: C, 37.00; H, 3.73; S, 59.28. Found: C, 37.20; H, 3.61; S, 59.37.

A solution of crude 3-butene-1,2-dithiol trithiocarbonate (10.73 g, 0.066 mol) in 50 ml of ether was added with stirring to a slurry of 3.8 g (0.10 mol) of $LiAlH_4$ in 100 ml of ether, and the mixture was stirred overnight at room temperature. The excess hydride was decomposed with water, and the mixture was acidified with 6 *N* HCl. The layers were separated and the aqueous layer was extracted with ether. The ether extracts were combined, washed with water, and dried ($MgSO_4$). The solvent was removed under reduced pressure to give 6.88 g (86%) of 3-butene-1,2-dithiol. Further attempts to purify the material resulted in decomposition.

A 2.4-g sample of 3-butene-1,2-dithiol was converted to **8** by reaction with acetone using the procedure described for the preparation of **7**. The product was obtained as a light yellow oil (3.05 g). Attempted distillation resulted in decomposition. It could be collected from glpc programmed from 50° up at 4°/min: ir (CCl_4) 3060, 2940, 2900, 1850, 1640, 1440, 1368, 1160, 984, and 919 cm^{-1}; nmr (CCl_4) δ 1.70 (6 H, s), 3.10 (2 H, m), 4.20 (1 H, m), and 4.8–6.0 ppm (3 H, m); mass spectrum *m/e* (rel intensity) 160 (15), 145 (32), 106 (77), 99 (10), 88 (10), 87 (15), 86 (98), 86 (66), 84 (31), 75 (31), 74 (26), 59 (100), 45 (26), 41 (22), and 39 (18).

Anal. Calcd for $C_7H_{12}S_2$: C, 52.44; H, 7.54; S, 40.00. Found: C, 52.28; H, 7.51; S, 40.05.

2,2,4,4-Tetramethyl-1,3-dithietane (9).—Assignment of structure to this product is based on its identity with **9** obtained from irradiation of 2,2-dimethyl-1,3-dithian-5-one[10] where the structural assignment was based on the following data: mp 77.0–77.5°; ir (KBr) 2990, 2950, 2920, 2850, 1460, 1450, 1380, 1160, 1135, 920, and 570 cm^{-1}; uv max (hexane) 234 nm (ϵ 138) and 302 (30); nmr (CCl_4) δ 1.87 (12 H, s); mass spectrum *m/e* (rel intensity) 150 (2), 149 (2), 148 (10), 74 (55), 59 (100), and 41 (17).

Anal. Calcd for $C_6H_{12}S_2$: C, 48.59; H, 8.15; S, 43.24. Found: C, 48.81; H, 8.09; S, 43.15.

Diisopropyl Disulfide (10).—The authentic sample of **10** was purchased from Wateree Chemical Co.

3,3,5,5-Tetramethyltrithiolane (11).—A mixture of 58 g (1 mol) of acetone and 20 g of phosphorus pentasulfide was heated under reflux for 12 hr, poured onto crushed ice, and extracted with ether. The ether extract was dried ($MgSO_4$) and the solvent was removed under reduced pressure. The residue was distilled to obtain 12.4 g (7%) of **11**, bp 85–87° (18 mm) [lit.[11] bp 75° (10 mm)].

Cyclohexyl Isopropyl Sulfide (12).—A solution of sodium ethoxide was prepared by dissolving 9.2 g (0.4 g-atom) of Na in 250 ml of ethanol. A dewar condenser was attached to the flask and 30.4 g (0.4 mol) of isopropyl mercaptan was slowly added to the solution with stirring. To this solution was added 65.2 g (0.4 mol) of cyclohexyl bromide in 100 ml of ethanol. A cloudy white precipitate formed almost immediately. The mixture was refluxed for 12 hr. The solution was cooled, water (400 ml) was added, and the mixture was extracted with pentane. The pentane extracted was dried ($MgSO_4$), and the solvent was removed under reduced pressure. Distillation of the residue afforded 9.04 g (14%) of **12**: bp 121–122° (35 mm); ir (CCl_4) 2960, 1453, 1387, 1340, 1247, 1205, 1168, 1055, 1000, and 890 cm^{-1}; nmr (CCl_4) δ 1.20 (6 H, d), 1.2–2.6 (11 H, m), and 2.90 ppm (1 H, septet).

Anal. Calcd for $C_9H_{18}S$: C, 68.28; H, 11.46; S, 20.25. Found: C, 68.10; H, 11.28; S, 20.36.

1,6-Dithiaspiro[6.5]undec-3-ene (14).—Mercaptole **14** was prepared in 48% yield from cyclohexanone and *cis*-2-butene-1,4-dithiol by the same procedure described for the preparation of **7**: bp 117° (1.0 mm); ir (CCl_4) 3010, 2910, 2845, 1440, 1396, 1265, and 1005 cm^{-1}; uv max (cyclohexane) 248 nm (ϵ 3120) and 280 (639); nmr (CCl_4) δ 1.4–2.2 (10 H, m), 3.2–3.5 (4 H, m) and 5.4–5.9 ppm (2 H, m); mass spectrum *m/e* (rel intensity) 200 (28), 146 (32), 135 (10), 114 (16), 85 (16), 82 (10), 81 (100), 71 (13), 55 (12), 45 (15), 41 (13), and 39 (14).

Anal. Calcd for $C_{10}H_{16}S_2$: C, 59.94; H, 8.05; S, 32.01. Found: C, 60.06; H, 7.96; S, 32.03.

2-Vinyl-1,4-dithiaspiro[4.5]decane (15).—Mercaptole **15** was prepared from cyclohexanone and 3-butene-1,2-dithiol by the procedure described for the preparation of **8**. Attempted purifi-

(5) The internal standards used were *n*-$C_{12}H_{26}$ (The Matheson Co.), *n*-$C_{14}H_{30}$, *n*-$C_{15}H_{32}$, *n*-$C_{16}H_{34}$, *n*-$C_{17}H_{36}$, or *n*-$C_{18}H_{38}$ (Aldrich Chemical Co.).

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cation by distillation resulted in decomposition. Purification could be effected by collection from glpc: ir (CCl_4) 3075, 2918, 2845, 1840, 1658, 1630, 1442, 1262, 1118, 980, and 916 cm^{-1}; mass spectrum *m/e* (rel intensity) 200 (12), 157 (47), 146 (39), 115 (51), 86 (58), 81 (100), and 71 (32).

Anal. Calcd for $C_{10}H_{16}S_2$: C, 59.92; H, 8.05. Found: C, 59.86; H, 7.86.

7,14-Dithiadispiro[5.1.5.1]tetradecane (16), Dicyclohexyl Disulfide (17), and Dicyclohexyl Sulfide (18).—The structures of products **16–18** were established by spectral comparison with material reported previously.[3]

1,5-Dihydro-2,4-benzodithiepin (19).—To a solution of 112.5 g (0.426 mol) of α,α'-dibromo-*o*-xylene (Aldrich Chemical Co.) in 200 ml of ethanol was added 56.4 g (0.752 mol) of thiourea and the mixture heated under reflux for 5 hr. A solution of 50 g of NaOH in 500 ml of water was added and the solution was heated under reflux for an additional 2 hr. The mixture was cooled, acidified with 6 *N* HCl, and extracted with ether. The ethereal extract was washed with water and dried ($MgSO_4$). The solvent was removed and the residue was distilled under reduced pressure to give 54.1 g (75%) of 1,2-benzenedimethanethiol, bp 105–107° (0.25 mm) [lit.[8] bp 160° (20 mm)].

To 15.0 g of a 40% aqueous solution of formaldehyde was added 34.0 g (0.187 mol) of 1,2-benzenedimethanethiol followed by 10 ml of concentrated HCl. The solution was stirred for 10 min, ether was added, and the precipitate which formed was collected by filtration. The product was sublimed at 45° (0.05 mm) to give 22.5 g (62%) of white crystals: mp 155–156° (lit.[8] mp 152–153°); ir ($CHCl_3$) 2985, 2900, 1494, 1455, 1430, 1380, 1150, and 895 cm^{-1}; uv max (cyclohexane) 255 nm (ϵ 1550); nmr ($CDCl_3$) δ 3.90 (2 H, s), 4.00 (4 H, s) and 7.28 (4 H, s); mass spectrum *m/e* (rel intensity) 182 (42), 136 (15), 135 (100), 134 (14), 104 (28), and 91 (14).

1,3-Dihydroisothionaphthene (20).—Product **20** was prepared in 55% yield in these laboratories by Dr. A. L. Maycock as previously described,[12] bp 49–57° (0.5 mm) [lit.[12] bp 94.7° (5 mm)].

Isothiochromane (21).—Compound **21** was prepared in 57% yield from 4-oxoisothiochromane as previously reported,[13] bp 65–66° (0.4 mm) [lit.[13] bp 129° (13 mm)].

1,2,4-Trithiolane (22).—The structure of **15** was established by comparison of its mass spectrum with that which is published.[14]

1,5-Dihydro-3,3-dimethyl-2,4-benzodithiepine (23).—To 14.1 g (0.083 mol) of 1,2-benzenedimethanethiol was added 10 ml of acetone, and HCl gas was passed through the mixture at a rapid rate. A white milky precipitate formed immediately and crystallized when water was added. The product was collected by filtration, dried, and sublimed at 60° (0.5 mm) to give 12.5 g (72%) of white crystals: mp 136–137°; ir ($CHCl_3$) 2970, 2920, 2850, 1492, 1450, 1439, 1380, 1365, 1160, and 1147 cm^{-1}; uv max (cyclohexane) 252 nm (ϵ 1490); nmr ($CDCl_3$) δ 1.74 (6 H, s), 3.92 (4 H, s) and 7.15 ppm (4 H, s); mass spectrum *m/e* (rel intensity) 210 (13), 136 (31), 135 (100), 134 (17), 106 (12), 104 (17), 91 (17), and 59 (12).

3,4-Benzo-1,6-dithiaspiro[6.5]undecane (24).—Mercaptole **24** was prepared from 25.5 g (0.15 mol) of 1,2-benzenedimethanethiol, 19.6 g (0.20 mol) of cyclohexanone, and 0.020 g of *p*-toluenesulfonic acid by the same procedure described for the preparation of **7** except that the reflux period was 7 hr. After the solvent was removed the solid was shaken with 2 l. of ether. The ether was filtered, concentrated, and cooled in the refrigerator. The mercaptole crystallized and was collected by filtration in a yield of 16.6 g (43%), mp 95–98°. An additional recrystallization from ether gave mp 96.5–98°; ir ($CHCl_3$) 3055, 3010, 2920, 2845, 1492, 1445, 1395, 1250, 1185, and 1008 cm^{-1}; uv max (cyclohexane) 231 nm (ϵ 4580) and 254 (1290); nmr ($CDCl_3$) δ 1.40–1.80 (6 H, m), 1.90–2.10 (4 H, m), 3.94 (4 H, s), and 7.15 ppm (4 H, s); mass spectrum *m/e* (rel intensity) 250 (16), 217 (17), 136 (35), 135 (100), 115 (18), 105 (19), 91 (17), and 81 (31).

Anal. Calcd for $C_{14}H_{18}S_2$: C, 67.15; H, 7.25; S, 25.61. Found: C, 67.23; H, 7.31; S, 25.50.

Cyclohexyl Mercaptan (25).—The authentic sample of **25** was purchased from Aldrich Chemical Co.

2,2-Dimethyl-1,3-benzodithiin (28).—To a slurry of 24 g (0.634 mol) of lithium aluminum hydride in 1000 ml of tetrahydrofuran was added, dropwise with stirring, 92.0 g (0.5 mol) of 2,3-dithiosulfindene[15] in 100 ml of tetrahydrofuran. The mixture was stirred for 8 hr at room temperature. The excess hydride was decomposed with water, and the mixture acidified with 6 *N* HCl. Water (1 l.) was added and the mixture was extracted with ether. The ether extract was washed with water and dried ($MgSO_4$), and the ether was removed under reduced pressure. The residue was distilled to give 73.7 g (94%) of *o*-α-toluenedithiol, bp 90–92° (0.5 mm) [lit.[16] bp 125–126° (12 mm)].

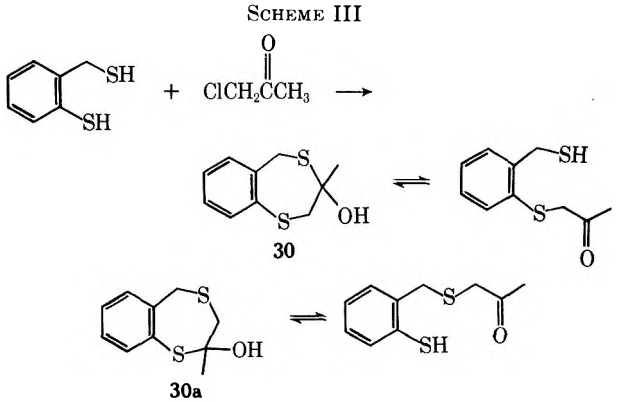
Mercaptole **28** was prepared in 85% yield from 5.84 g (0.0374 mol) of *o*-α-toluenedithiol and 3.0 g (0.0517 mol) of acetone in 30 ml of benzene by the procedure described for the preparation of **7**: bp 78–82° (0.2 mm) [lit.[16] bp 140–141° (12 mm)]; ir (CCl_4) 3065, 2965, 2920, 1570, 1472, 1450, 1386, 1368, 1160, 1110, and 1070 cm^{-1}; uv max (cyclohexane) 232 nm (ϵ 5740) and 262 (4920); nmr ($CDCl_3$) δ 1.59 (6 H, s), 3.68 (2 H, s), and 7.18–7.30 ppm (4 H, m); mass spectrum *m/e* (rel intensity) 196 (100), 181 (18), 163 (60), 153 (25), 122 (98), 78 (24), 77 (15), 59 (16), and 39 (10).

5,6-Benzo-1,4-dithia-2-hydroxy-2-methylcycloheptane (30).—To a solution of 15.6 g (0.10 mol) of *o*-α-toluenedithiol in 100 ml of anhydrous ether was added 2.30 g of Na metal and a small amount of methanol. After the Na was dissolved, chloroacetone (9.25 g, 0.10 mol) was slowly added and the solution was stirred for 8 hr. Water was added and the mixture was extracted with ether. The ether extract was dried ($MgSO_4$) and the ether was removed under reduced pressure. The white crystalline residue (20.2 g, 95%) was recrystallized from CCl_4: mp 95–98°; ir ($CHCl_3$) 3460, 2960, 1409, 1330, 1200, 1070, and 900 cm^{-1}; nmr ($CDCl_3$, room temperature) δ 1.62 (3 H, s), 3.05 (2 H, s), 3.50 (1 H, d, J = 15 Hz), 4.57 (1 H, d, J = 15 Hz), 4.48 (1 H, s), and 7.10–7.80 ppm (4 H, m); nmr (C_2Cl_4, 112°) δ 1.78 (1 H, t, J = 8 Hz), 2.11 (3 H, s), 3.57 (2 H, s), 3.88 (2 H, d, J = 8 Hz), and 6.9–7.7 ppm (4 H, m); mass spectrum *m/e* (rel intensity) 212 (2), 194 (35), 160 (70), 156 (22), 154 (55), 153 (100), 135 (41), 134 (11), 123 (20), 122 (35), 121 (34), 91 (20), 77 (15), 76 (30), 68 (14), 45 (36), and 39 (14).

Anal. Calcd for $C_{10}H_{12}OS_2$: C, 56.57; H, 5.70; S, 30.19. Found: C, 56.05; H, 5.86; S, 29.02. Further attempts at purification did not improve the purity.

The product from the reaction of *o*-α-toluenedithiol and chloroacetone in the presence of 1 equiv of base existed initially in the cyclic form (**30**) at room temperature (see Scheme III) but was

SCHEME III



converted in solution to the mercapto ketone form on heating in tetrachloroethylene. The ring opening was observed from the nmr spectrum and established the structure as **30** rather than **30a** since the spectrum at 112° showed absorption for the SH hydrogen atom as a triplet (J = 8 Hz) at 1.78 and the benzylic hydrogen atoms as a doublet (J = 8 Hz) at 3.88 ppm.

5,6-Benzo-1,4-dithia-2-methylcycloheptene (29).—To a solution of 2.12 g (0.01 mol) of **30** in 40 ml of pyridine was added slowly 2.5 g of $POCl_3$. The mixture was stirred at room temperature for 5 hr, and the solution was poured onto crushed ice. The aqueous mixture was extracted with ether. The ether extracts were washed with 6 *N* HCl and water and dried ($MgSO_4$). Removal of the solvent gave 1.49 g (77%) of white, crystalline 5,6-benzo-1,4-dithia-2-methylcycloheptene that was sublimed

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at 80° (0.1 mm): mp 100–102°; ir (CCl_4) 3040, 2980, 2945, 1575, 1468, 1438, 1413, 1286, 1200, and 1088 cm^{-1}; nmr ($CDCl_3$) δ 1.80 (3 H, d, J = 1.2 Hz), 4.50 (2 H, s), 5.78 (1 H, q, J = 1.2 Hz), and 7.2–7.6 ppm (4 H, m); mass spectrum m/e (rel intensity) 194 (34), 162 (12), 161 (100), 153 (18), 135 (59), 134 (15), 121 (11), 90 (15), 77 (12), 59 (12), and 45 (12).

Anal. Calcd for $C_{10}H_{10}S_2$: C, 61.81; H, 5.19; S, 33.01. Found: C, 61.75; H, 5.13; S, 33.18.

To a solution of 97 mg (5.0 mmol) of the above olefin in 50 ml of ethanol was added 388 mg of palladium-on-carbon catalyst (Matheson). The flask was equipped with a magnetic stirrer and placed under 1 atm of hydrogen. After 12 hr, 300 mg of catalyst was added, and the material was hydrogenated for an additional 12 hr. The catalyst was removed by filtration with the aid of Celite and washed with hot methanol, and the solvent was removed under reduced pressure. The residue contained starting olefin and **29** (13% yield) that was collected from glpc (LAC-446): ir (CCl_4) 3060, 2962, 2905, 1470, 1440, 1410, 1372, 1238, 1152, and 1000 cm^{-1}; nmr ($CDCl_3$) δ 1.29 (3 H, d, J = 7 Hz), 2.36–3.40 (3 H, m), 3.74 (1 H, d, J = 15 Hz), 4.18 (1 H, d, J = 15 Hz), and 7.0–7.7 ppm (4 H, m); mass spectrum m/e (rel intensity) 196 (100), 155 (19), 154 (64), 153 (72), 150 (25), 136 (24), 135 (57), 121 (22), 91 (15), 78 (10), 77 (22), 45 (14), 44 (12), 40 (13), and 39 (13).

Anal. Calcd for $C_{10}H_{12}S_2$: C, 61.18; H, 6.16; S, 32.66. Found: C, 61.27; H, 6.22; S, 32.86.

2,3-Benzo-1,5-dithiaspiro[5.5]undecane (31).—Mercaptole **31** was prepared in 74% yield from 9.2 g (0.104 mol) of cyclohexanone and 15.6 g (0.10 mol) of *o*-α-toluenedithiol by the same procedure described for the preparation of **7**: bp 120–124° (0.07 mm); ir (CCl_4) 3065, 2940, 2860, 1570, 1470, 1450, 1272, 1120, and 1012 cm^{-1}; uv (cyclohexane) 231 nm (ε 6000), 263 (469); nmr ($CDCl_3$) δ 1.4–2.0 (10 H, m), 3.71 (2 H, s), and 6.95–7.4 ppm (4 H, m); mass spectrum m/e (rel intensity) 237 (15), 236 (100), 203 (57), 193 (21), 154 (10), 153 (26), 147 (15), 123 (84), 121 (26), 81 (12), 78 (10), and 45 (10).

Anal. Calcd for $C_{13}H_{16}S_2$: C, 66.05; H, 6.82; S, 27.13. Found: C, 65.91; H, 6.89; S, 26.98.

***cis*-2,3-Benzo-1,5-dithiabicyclo[5.4.0]undecane (32).**—The identification of **32** is based slowly on spectral data: ir (CCl_4) 3050, 2910, 2840, 1470, 1443, 1408, 1268, and 1005 cm^{-1}; mass spectrum m/e (rel intensity) 226 (30), 203 (10), 155 (17), 154 (70), 153 (100), 124 (12), 123 (19), 122 (11), 121 (17), 109 (10), 81 (17), 77 (22), 45 (12), 41 (12), 40 (13), and 39 (19).

2,3-Benzo-1,4-dithiaspiro[4.5]decane (33).—Mercaptole **33** was prepared in 55% yield from 2.60 g (26 mmol) of cyclohexanone and 3.55 g (25 mmol) of 1,2-benzenedithiol by the procedure described for the preparation of **7**: bp 120–123° (0.25 mm); ir (CCl_4) 3040, 2910, 2840, 1440, 1254, 1112, 1005, and 975 cm^{-1}; uv max (cyclohexane) 238 nm (ε 12,100), 273 (3070), 292 (2220), 302 (2100), and 312 (1600); nmr (CCl_4) δ 1.3–1.9 (6 H, m), 2.1–2.4 (4 H, m) and 7.05 ppm (4 H, m); mass spectrum m/e (rel intensity) 222 (45), 179 (100), 166 (17), 153 (8), 81 (8), and 77 (7).

Anal. Calcd for $C_{12}H_{14}S_2$: C, 64.81; H, 6.35; S, 28.84. Found: C, 65.03; H, 6.42; S, 29.08.

***cis*-3,4-Benzo-2,5-dithiabicyclo[4.4.0]decane (34).**—To a solution of 416 mg (2.81 mmol) of *cis*-1,2-cyclohexanedithiol[3] in 50 ml of ethanol was added 393 mg (2.75 mmol) of cuprous oxide. The mixture was heated under reflux for 40 hr, cooled, and filtered. The red cuprous salt was dried and dissolved in 25 ml of quinoline containing 5 ml of pyridine. *o*-Dibromobenzene (589 mg, 2.5 mmol) was added and the mixture was heated under reflux for 12 hr. The solution was cooled and poured into a stirred mixture of ice and hydrochloric acid. The mixture was stirred 2 hr and extracted with ether. The ether extracts were washed with 3 *N* HCl, 10% $NaHCO_3$, and water and dried ($MgSO_4$). After removal of the solvent, the product (14% yield) was collected by glpc: ir (CCl_4) 3060, 2940, 2860, and 1460 cm^{-1}; nmr (CCl_4) δ 1.4–2.2 (8 H, m), 3.3–3.7 (2 H, m), and 6.9–7.1 ppm (4 H, m); mass spectrum m/e (rel intensity) 222 (100), 179 (27), 153 (23), 142 (35), 140 (80), 96 (19), 81 (59), 80 (20), 79 (10), 77 (12), 41 (13), and 39 (12).

Anal. Calcd for $C_{12}H_{14}S_2$: C, 64.82; H, 6.35. Found: C, 65.29; H, 6.49.

Registry No.—**3**, 4479-55-4; **5**, 4410-13-3; **7**, 14198-71-1; **8**, 31443-07-9; **9**, 31443-08-0; **12**, 7133-39-3; **14**, 31443-10-4; **15**, 31443-11-5; **19**, 7216-19-5; **23**, 14198-73-3; **24**, 31443-14-8; **28**, 6247-53-6; **29**, 31443-21-7; **30**, 31442-16-0; **31**, 31443-17-1; **32**, 31443-18-2; **33**, 7127-65-3; **34**, 31443-19-3; 3-butene-1,2-dithiol trithiocarbonate, 31443-20-6.

Photocyclization of Acrylanilides[1]

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Received April 2, 1971

Ultraviolet irradiation of acrylanilides (I) has been found to afford a cyclization product, 3,4-dihydrocarbostyrils (II); *e.g.*, methacrylanilide (Ib) in *n*-hexane gives IIb in a quantum yield of 0.26 and *N*-methylmethacrylanilide (Id) gives IId in a quantum yield of 0.24. The sensitizing and quenching studies suggest that the reaction occurs *via* an excited singlet state and that the formation of an enol precursor IV is less favorable. Their quantum yields tend to decrease with increasing solvent polarity, which is attributable to an increase of the efficiency of intersystem crossing with increasing the polarity of solvent.

It is known that the photolysis of *N*-phenylacylamides undergoes acyl migration to *o*- and *p*-acylanilines,[2-4] but that acrylanilides with an α,β-unsaturated acyl group photocyclize[5] without rearrangement except in the case of benzanilides which give both rearranged and cyclized products.[6]

Ultraviolet irradiation of *N*-allylanilines affords mainly anilines together with small amounts of ortho and para rearranged products.[7] However, *N*-allylaniline gives a cyclized product, *i.e.*, quinoline, in the presence of oxidizing agents such as $FeCl_3 \cdot 6H_2O$. Similarly, photolysis of aryl acrylates gives *o*- and *p*-acrylphenols without cyclization to lactones.[8]

(1) Contribution No. 168.

(2) (a) For the review of the photo-Fries rearrangement see D. Bellus and P. Hrdlovic, *Chem. Rev.*, **67**, 599 (1967); (b) J. C. Anderson and C. B. Reese, *J. Chem. Soc.*, 1781 (1963); (c) H. Kobsa, *J. Org. Chem.*, **27**, 2293 (1962); (d) R. A. Finnegan and A. W. Hagen, *Tetrahedron Lett.*, 365 (1963); (e) Y. Ogata, K. Takagi, and I. Ishino, *Tetrahedron*, **26**, 2703 (1970).

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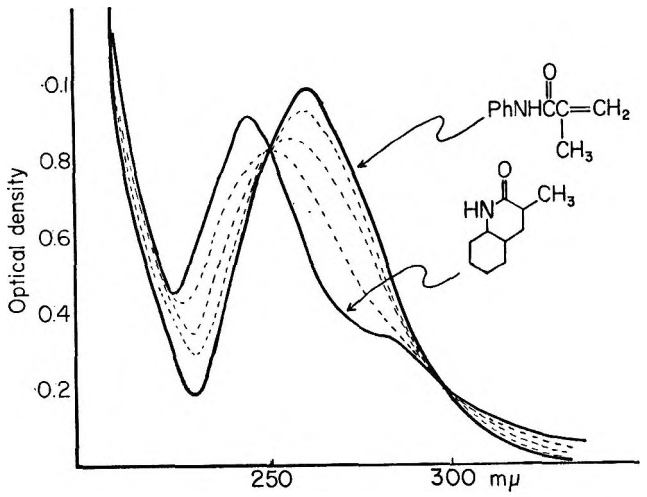


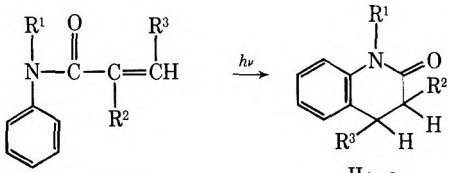
Figure 1.—Spectral changes of methacrylanilide in ethyl ether with lapse of the time on irradiation with 2537-Å light (at room temperature).

N-Allyl- and *N*-benzylanilines are easily oxidized to the corresponding conjugated imines, *i.e.*, *N*-allylideneaniline and *N*-benzylideneaniline, respectively;[9] hence the photocyclization of *N*-allylaniline to quinoline by $FeCl_3$ may proceed through oxidation to *N*-allylideneaniline. Also an α,β-unsaturated aromatic imine such as *N*-cinnamylideneaniline was observed to undergo cyclization.[10] These facts suggest for the photocyclization of acrylanilides a pathway involving α,β-unsaturated aromatic imines.

The present paper proposes a mechanism for the photocyclization of some acrylanilides and presents a discussion on the solvent effect and the nature of the excited state.

Results and Discussion

Uv irradiation of acrylanilide (Ia) in benzene (10^{-2} *M*) afforded 3,4-dihydrocarbostyril (IIa, 4.0%) together with a small amount of aniline and some other products. The identification of products was done by their melting points, ir, uv, and glc in comparison with the authentic samples.



IIa–e

Ia, $R^1 = R^2 = R^3 = H$
b, $R^1 = R^3 = H$; $R^2 = Me$
c, $R^1 = R^2 = H$; $R^3 = Ph$
d, $R^1 = R^2 = Me$; $R^3 = H$
e, $R^1 = Me$, $R^2 = R^3 = H$

The spectrum of the solution of methacrylanilide changed markedly on irradiation with 2537-Å light as shown in Figure 1. The absorption maximum at 260 mμ of Ib decreased and a new band with a maximum at 240 mμ of IIb appeared with two isosbestic points at 250 and 297 mμ as the reaction proceeded.

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Photolysis of *N*-methylmethacrylanilide (Id) in benzene (2×10^{-2} *M*) gave *N*-methyl-3-methyl-3,4-dihydrocarbostyril (IId, 57.0%) and a small amount of *N*-methylaniline. Its identity was established as follows. The nmr spectrum of the product (IId) showed aromatic protons (τ 3.0, m, 4 H), NCH_3 (τ 6.75, s, 3 H), methyl and methine protons (τ 7.3, m, 3 H), and CCH_3 (τ 8.56, d, 3 H). The characteristic carbonyl absorption of lactam (liquid film) was observed at 1660 cm^{-1}.

No photorearrangement of Ia–e to *o*- and *p*-acrylanilides was observed. Furthermore, cinnamylanilide (Ic) and *N*-methylacrylanilide (Ie) undergo neither cyclization nor rearrangement, but polymerization alone.

Solvent Effect.—The photocyclization is much affected by the nature of solvents used. Table I lists the yields of photoproducts of methacrylanilide (Ib) and *N*-methylmethacrylanilide (Id) in acetonitrile, methanol, 2-propanol, acetone, *n*-propyl bromide, diethyl ether, benzene, and *n*-hexane as solvents. Apparently, the ratio of products depends on the nature of the solvent polarity.

TABLE I
PHOTOLYSIS OF METHACRYLANILIDE IN VARIOUS SOLVENTS[a]

Solvent	Dielectric constant	Viscosity, cP (25°)	Recovered,[b] %	Product, %	Quantum yield
CH_3CN	37.5	0.33	89.4	None	
CH_3OH	32.6	0.55	96.6	None	<0.01
$(CH_3)_2C=O$	20.7	0.30	80.6	None	
i-PrOH	18.3	1.76	96.0	None	
n-PrBr	8.1	0.46	60.1	22.3	
EtOEt	4.34	0.24	55.5	24.3	0.23
C_6H_6	2.28	0.65	53.4	33.0	
n-C_6H_{14}[c]	1.09	0.29	17.7	63.5	0.26

[a] Concentration of 4.0×10^{-2} *M* except for the case of *n*-hexane. [b] Irradiation time 8 hr with a 300-W light high-pressure Hg lamp in a Pyrex tube. [c] Concentration of 9.0×10^{-5} *M* with irradiation time 5 min.

The quantum yield for the formation of IIb did not increase even in acetone, which is known as an efficient triplet sensitizer. This result suggests that the reaction does not proceed *via* an excited triplet state. The effect is ascribed to an increase of the rate of intersystem crossing by increasing the spin orbital coupling in polar solvents, because the quantum yields do not correlate with any other factors such as viscosity, hydrogen-bonding ability, etc.

Reaction Multiplicity.—For the clarification of multiplicity in the cyclization the following quenching and sensitizing experiments were carried out.

A plot of the ratio of the quantum yields of Ib in the absence and presence of quencher (1,3-pentadiene) (Φ_0/Φ) against the quencher concentration shows the independence of Φ_0/Φ on the quencher concentration, which means the lack of quenching (Figure 2). No sensitization by acetophenone (E_T = 73.6 kcal/mol) and benzophenone (E_T = 68.5 kcal/mol) was observed under conditions in which over 99% of incident light of wavelength longer than 330 mμ was absorbed. Although the phosphorescence of benzophenone was not quenched by Ib and Id, those of acetophenone and acetone were efficiently quenched by Ib and Id; hence

the energy transfer from the latter sensitizer to substrates (Ib and Id) is probable (Table II). Therefore,

TABLE II

QUENCHING OF SENSITIZER PHOSPHORESCENCE BY ANILIDES

Sensitizer	E_T, kcal/mol	Anilides (M)	I_{rel}[c]
Benzophenone,	68.5	None	1.00
1.0×10^{-3} M,		MAA (1×10^{-4})[a]	1.08
λ_{max} 442 mμ		NMAA (1×10^{-4})[b]	1.05
Acetophenone,	76.3	None	1.00
1.0×10^{-2} M,		MAA (1×10^{-3})	0.28
λ_{max} 414 mμ		NMAA (1×10^{-3})	0.35
Acetone,	78	None	1.00
0.2 M,		MAA (1×10^{-2})	0.29
λ_{max} 440 mμ		NMAA (1×10^{-2})	0.30

[a] MAA, methacrylanilide. [b] NMAA, *N*-methylmethacrylanilide. [c] I_{rel} is the relative intensity of the phosphorescence maximum. Excitation wavelength is 280 mμ for acetone, 350 mμ for acetophenone, and 360 mμ for benzophenone.

the cyclization occurs *via* an excited singlet state, but not *via* an excited triplet state. Additionally, the sensitization study indicates that the triplet energy of Ib and Id is between 68.5 and 74 kcal/mol.

Emission Spectra.—Excited states of anilides were examined by means of their fluorescence emission spectra in various solvents as listed in Table III. The

TABLE III

FLUORESCENCE SPECTRA OF METHACRYLANILIDE AT 290 mμ

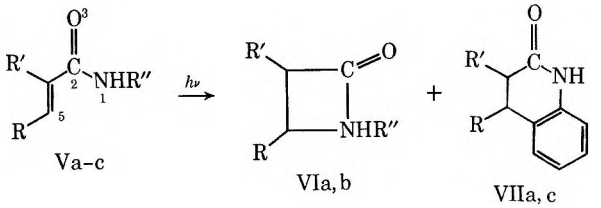
Solvent	Fluorescence (at room temperature) λ_{max}	I_{rel}[a]
n-Hexane	318	0.1
Ethyl ether	320	1.0
Methanol	328	2.4

[a] I_{rel} is the relative intensity of the fluorescence maximum. The concentration was adjusted so that the optical density at 290 mμ is 0.400.

emission maxima shift bathochromically in polar solvents. This fact indicates that the lowest excited singlet state is π–π^*, as observed with other anilides.[3] Therefore, the fluorescence may be due to the emission in falling from S_1 (π–π^*) to S_0.

Our attempt to examine phosphorescence emission in various rigid glasses at 77°K failed. However, the lowest triplet electronic state may also be π–π^* in view of the less efficient photoreduction of anilides by isopropyl alcohol and the π–π^* character of the lowest triplet state reported with acetanilide.[3]

Reaction Pathways.—α,β-Unsaturated amides were reported to be photocyclized to the corresponding β-lactams and/or the corresponding dihydrocarbostyrils.[5]



Va-c VIa,b VIIa,c

a, R = R′ = R″ = Ph
b, R = R′ = Ph; R″ = H
c, R = R′ = Me; R″ = Ph

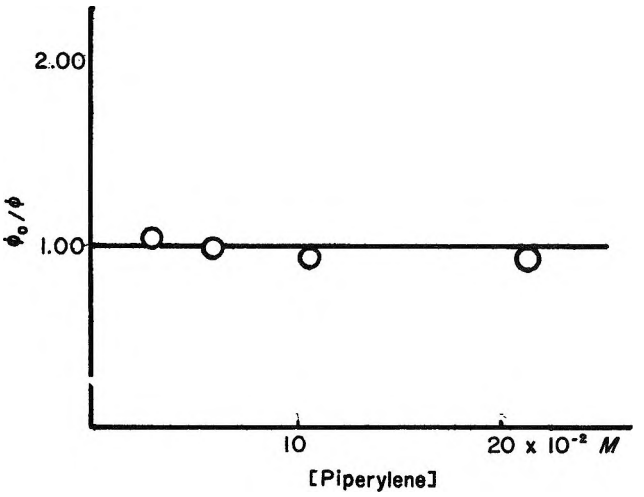
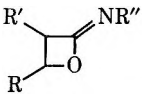


Figure 2.—Stern–Volmer plot of the quenching of methacrylanilide by piperylene in ether at room temperature.

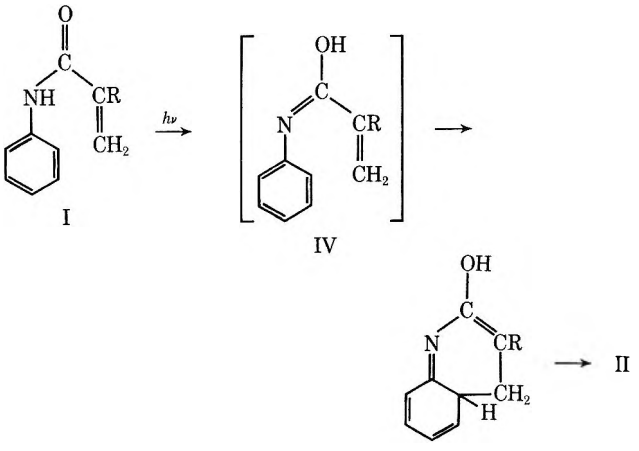
The β-lactam formation from Va and Vb was predicted by means of HMO calculations,[5] but the predicted formation of iminolactone VIII from Vb was incorrect. Hence bonding between 1 and 5 atoms is



VIII

preferred to that between 3 and 5 atoms. The 1,5 bonding may occur by way of enolization as shown in Scheme I (one-electron transfer of a nonbonding electron on N to the excited carbonyl oxygen atom[11–13] followed by proton migration). Moreover, our HMO calculations indicate that 1,5 bonding of the enol intermediate of the amide (Vb) is more favorable than the 1,3 bonding on excitation; *i.e.*, the 1,5 bond order is equal to +0.06370 and the 1,3 bond order to +0.03876 on excitation (Scheme I).

SCHEME I



(11) (a) S. G. Cohen and J. B. Guttenplan, *J. Amer. Chem. Soc.*, **89**, 164 (1967); (b) S. G. Cohen and H. M. Chao, *ibid.*, **90**, 165 (1968); (c) S. G. Cohen and J. B. Guttenplan, *Tetrahedron Lett.*, 5353 (1968); (d) S. G. Cohen, M. D. Daltzman, and J. B. Guttenplan, *ibid.*, 4321 (1969); (e) S. G. Cohen and G. I. Cohen, *J. Phys. Chem.*, **72**, 3782 (1968).

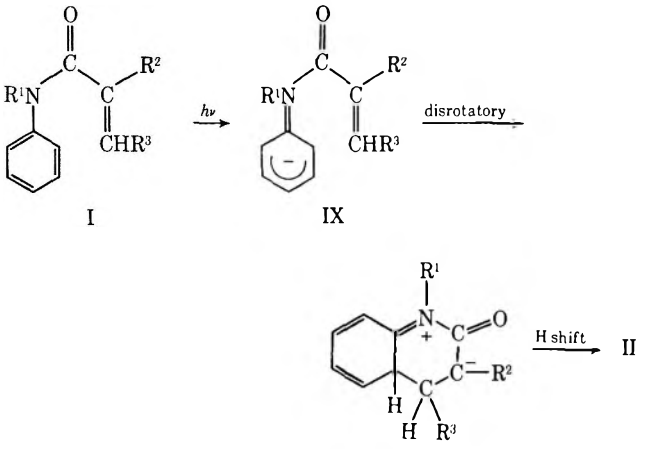
(12) A. Padwa, W. Eisenhardt, R. Gruber, and D. Pashayan, *J. Amer. Chem. Soc.*, **91**, 1857 (1969).

(13) P. J. Wagner and A. E. Kempanen, *ibid.*, **91**, 3085 (1969).

However, this scheme is unlikely, because (i) two isosbestic points at 250 and 297 mμ in Figure 1 indicate that the I → II photoconversion is void of a competitive or consecutive reaction; (ii) the *N*-methyl compound (Id, without N–H bond) cyclizes in high yield (Table I); and (iii) the esr signal of biradical could not be detected.

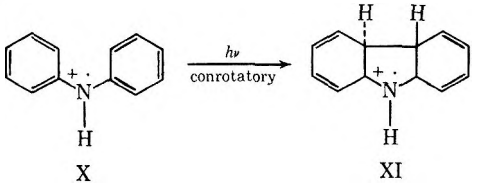
An alternative mechanism is presented in Scheme II, which involves formation of a charge-transfer intermediate (IX) indicated by the 250-mμ light absorption of the anilino ring followed by the seven-π-electrocyclic reaction in a disrotatory motion.

SCHEME II



This electrocyclization fits the Woodward–Hoffmann rule,[14] because most concerted reactions occur by way of a singlet state. Cyclization of a system of odd electrons ($n - 1$) of which IX is an example follows the rules for a system of even electrons (n) which has one more electron, if the highest occupied molecular orbitals are operative.

Thus, a five-π-electron system such as the radical cation of diphenylamine (X) cyclizes in a conrotatory motion to a hydrocarbazol species (probably trans ion XI) as a result of symmetry-allowed excited-state process.[15]



Experimental Section

Ir spectra were measured by the method of liquid film (or KBr disk) with a Perkin-Elmer ir spectrophotometer, Model 337; uv spectra were measured by a Hitachi double-beam spectrophotometer, Model 124; nmr spectra were measured by a Japan Electron Optic Laboratory Co. C60 HL high resolution nmr instrument. Quantitative analysis of photolysates was done by a Yanagimoto gas chromatograph with a flame ionization detector, Model GCG-550F, employing a 1.0 m × 2.5 mm column packed with PEG 20 M (5.0 wt %) on Chamelite CS of 80–100 mesh using N_2 as a carrier gas at 120–240°.

Materials.—Anilides[16] were prepared by the condensation of anilines and acyl halides in yields of 40–60%: acrylanilide (Ia),[16] mp 104° (lit.[16] 104–105°); methacrylanilide (Ib),[16] mp 86° (lit.[16] 87°), λ_{max}^{ether} 260 mμ (log ε 3.95); cinnamic anilide (Ic),[16] mp 154–156°, λ_{max}^{MeOH} 293 mμ; *N*-methylacrylanilide (Ie),[16] mp 74–75° (lit.[16] 75°), λ_{max}^{ether} 245 mμ; *N*-methylmethacrylanilide (Id),[16] mp 57° (lit.[16] 57°), λ_{max}^{ether} 242 mμ (log ε 3.85). Authentic 3,4-dihydrocarbostyril (IIa)[17] was prepared by $AlCl_3$-catalyzed intramolecular alkylation of β-chloropropionylanilide at 130–140° (45%), mp 165–166° (lit.[17] 165–166°), λ_{max}^{MeOH} 250 mμ (log ε 4.07).

Commercial *n*-hexane was purified by rectification after treatment with H_2SO_4, NaOH, and Na, bp 34.0–34.5°. Ethyl alcohol was rectified by treatment with concentrated H_2SO_4 and KOH, $AgNO_3$, and a silica gel column.

Light Source.—The irradiation was carried out using a Halos 300-W high pressure Hg lamp, which emits 3650–3663-Å light, and a Halos low-pressure Hg lamp emitting exclusively 2537-Å light.

Irradiation Procedure.—All experiments were carried out in a cylindrical quartz tube (20 × 150 and 10 × 200 mm) or a Pyrex tube (10 × 200 mm) under N_2 atmosphere except for preparative experiments.

Photolysis of Ia.—A solution of benzene (1 l.) containing Ia (2.0 g) was irradiated with a high-pressure Hg lamp for 150 hr at room temperature. Nitrogen was bubbled through the solution during the irradiation. The concentrated reaction mixture was chromatographed on a 20 × 450 mm column slurry packed in benzene with 100-mesh silica gel (Mallinckrodt), using benzene (500 cc) and then benzene–3% acetone (500 cc) as eluents. Fractions 30–40 (each 7 ml) were IIa (35 mg, 4%): mp 164–166°; λ_{max}^{MeOH} 250 mμ; ν_{max} 3170 (NH), 1680 (amide I, C=O), 1280, 1250 (amide III, CN), 2850, 2925 ($-CH_2-$), 3030, 1600, 1500 (aromatics), 1700–2000, 750 (ortho substitution); nmr spectrum showed aromatic protons (τ 3.0, m, 4 H), methylene protons (τ 7.3, A_2B_2 type, m, 4 H), NH (τ 0.4, 1 H). Fractions 56–70 were Ia (1.35 g), λ_{max}^{MeOH} 270 mμ, mp 104°.

Photolysis of Ib.—A solution of benzene (1 l.) containing Ib (1.80 g) was irradiated under N_2 with a high-pressure Hg lamp for 80 hr at room temperature. After irradiation, the solution was worked up as above. The concentrated reaction mixture was chromatographed on a 20 × 450 mm column slurry packed in benzene with 100 mesh silica gel (Mallinckrodt), using benzene (800 ml) as an eluent. Fractions 56–70 (each 7 ml) were IIb (1.09 g, 60.8%): mp 129–130°; λ_{max}^{MeOH} 250 mμ (log ε 3.93); ν_{max} 3175, 3070 (NH, cyclic lactam), 1680 (amide I, C=O), 1285 (amide III, CN), 3030, 1600, 1500 (aromatics), 1700–2000, 760 (monosubstitution), 2850, 2925 ($-CH_2-$, CH_3).

Photolysis of Id.—A solution of benzene (1 l.) containing Id (2.8 g) was irradiated under N_2 with a high-pressure Hg lamp for 80 hr at room temperature. After concentration by evaporation, the product mixture was chromatographed on a 20 × 450 mm column slurry packed in benzene with 100 mesh silica gel (Mallinckrodt), using benzene (800 cc) as an eluent. Fractions 43–68 (each 7 ml) were IId as a liquid (1.59 g, 57.0%): red-brown liquid; λ_{max}^{MeOH} 250 mμ (log ε 4.04); ν_{max} 1660 (amide I, C=O), 1230, 1305, 1115 (amide III, CN), 3050 (RCH, CH_2), 3020, 1580, 1450 (aromatics), 1700–2000, 765 (ortho substitution); nmr spectrum showed aromatic protons (τ 3.0, m, 4 H), NCH_3 (τ 6.75, s, 3 H), methylene and methine protons (τ 7.3, m, 3 H), CCH_3 (τ 8.56, d, 3 H). Fractions 77–100 were starting material (0.82 g).

Determination of Quantum Yield for Formation of 3,4-Dihydrocarbostyrils.—The quantum yields were determined by means of a liquid-phase chemical actinometer using potassium ferrioxalate at 15°. A low-pressure Hg lamp without filter was used as a light source, and produced 3,4-dihydrocarbostyrils were determined by uv spectrophotometry. A general procedure was as follows. A solution of 0.1–0.2 m*M* Ib in *n*-hexane was placed in a square quartz cell (path length 1 cm), degassed by four freeze–thaw cycles on a vacuum line, and sealed. A solution of 6.0 m*M* potassium ferrioxalate in 0.1 *N* H_2SO_4 was placed in an actinometer cell (path length 1 cm). Irradiation was continued for 5 min. The number of molecules of produced IIb in a cell was determined spectrophotometrically. The conversion of anilides (I) is less than 10% in all runs. The light intensity absorbed by the reactant was determined by the procedure reported by Parker and Hatchard.[18] The quantum yield was calculated from these data.

(14) R. B. Woodward and R. Hoffmann, "The Conservation of Orbital Symmetry," Academic Press, New York, N. Y., 1970.

(15) (a) R. A. W. Johnston and S. D. Ward, *J. Chem. Soc. C*, 1805 (1968); (b) M. J. Bishop and I. Freming, *ibid.*, 1712 (1969).

(16) M. Moureu, *Bull. Soc. Chim. Fr.*, (3) **9**, 421 (1898).

(17) F. Mayer, L. von Zutphen, and H. Philipps, *Ber.*, **60**, 858 (1927).

(18) (a) C. A. Parker, *Proc. Roy. Soc., Ser. A*, **220**, 104 (1953); (b) C. G. Hatchard and C. A. Parker, *ibid.*, **235**, 518 (1956).

Quenching Studies.—A solution (each 8 ml) containing a given concentration (4.0×10^{-2} *M*) of anilides and varying concentrations of 1,3-pentadiene was placed in a 10 × 150 mm Pyrex tube, degassed by four freeze–thaw cycles on vacuum line, and sealed. The tubes were irradiated by a Halos 300-W high-pressure Hg lamp on a rotating turntable apparatus immersed in a running water bath at 15°. The products were analyzed by glc.

Sensitizing Studies.—The irradiation was carried out for 50 hr at a 2:1 molar ratio of sensitizers to anilides. A Halos 300-W high-pressure Hg lamp with Toshiba UV-35 filter, which cut off light shorter than 3300 Å, was used as a light source.

Fluorescence and Phosphorescence Emission Studies.—The fluorescence spectra were measured on a Hitachi MPF-2A fluorescence spectrophotometer and the phosphorescence spectra were measured on the same apparatus with phosphorescence attachments. All phosphorescence spectra were recorded using EPA (ethyl ether–isopentane–ethanol, 5:5:2 volume ratio) as solvent. The solvent was checked for emission at each time when a spectrum was recorded. No interference due to emission of solvent was observed. The solutions contain *ca.* 10^{-3}–10^{-1} *M* solute and they formed clear glasses without microcrystals at 77°K.

Registry No.—Ia, 2210-24-4; Ib, 1611-83-2; Id, 15796-89-1; IIa, 553-03-7; IIb, 31883-79-1; IId, 31883-80-4; benzophenone, 119-61-9; acetophenone, 98-86-2; acetone, 67-64-1; *n*-hexane, 110-54-3; ethyl ether, 60-29-7; methanol, 67-56-1.

Acknowledgments.—The authors thank Dr. Y. Izawa for his helpful advice, Professor I. Kamiya and Dr. K. Aoki for their aid in measurement of emission spectra, and Dr. Y. Takahashi for the measurement of nmr spectra.

Cycloaddition of Benzyne to Substituted Cyclopentadienes and Cyclopentadienyl Grignard Reagents

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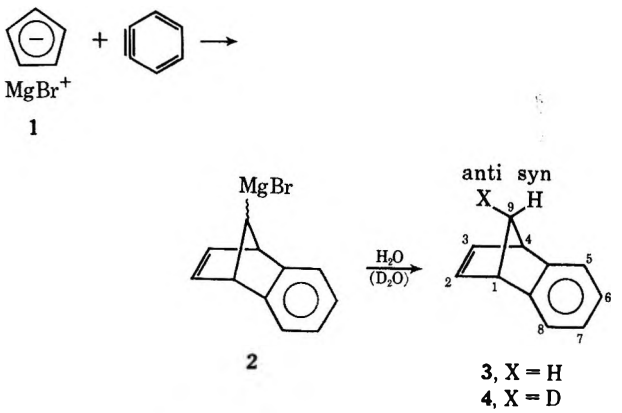
Received June 21, 1971

Benzyne was generated from 2-bromofluorobenzene and magnesium in tetrahydrofuran and added to isomeric mixtures of methylcyclopentadienes, 1,3-, 1,4-, and 2,5-dimethylcyclopentadienes, trimethylsilylcyclopentadienes, and *tert*-butylcyclopentadienes to give mixtures of substituted benzonorbornadienes whose isomeric distributions resembled those of the starting cyclopentadienes. Benzyne also was added to the corresponding cyclopentadienylmagnesium chlorides to give mixtures in which a 2-substituted benzonorbornadiene was always the major component. The intermediacy of 9-benzonorbornadienylmagnesium chlorides was demonstrated by stereospecific incorporation of one atom of D into the benzonorbornadienes by deuterolysis. The Grignard reactions may be described as $\pi^2s + \pi^4s$ cycloadditions, and their orientational selectivities are best explained by steric requirements in the transition state for cycloaddition.

The instability of benzyne makes it one of the most reactive dienophiles known in [2 + 4] cycloaddition and also makes it highly susceptible to nucleophilic addition, the ene reaction, insertion in carbon–hydrogen bonds, and other cycloadditions.[1] Additions of benzyne to cyclopentadiene and to cyclopentadienylmagnesium bromide (**1**) were first reported by Wittig and Knauss[2] to produce benzonorbornadiene (**3**,1,4-dihydro-1,4-methanonaphthalene) in 66 and 21% yields, respectively. Recently we[3] communicated that 9-benzonorbornadienylmagnesium bromide (**2**) was an intermediate in the addition of benzyne to **1** because deuterolysis of the reaction mixture produced benzonorbornadiene-*anti*-9-*d* (**4**). We described our results as the first well-established $\pi^2s + \pi^4s$ cycloadditions involving all-carbon anions. This paper describes additions of benzyne to cyclopentadienyl Grignards carried out to determine the influence of substitution on the course of cycloaddition. Concurrently, additions of benzyne to mixtures of isomeric substituted cyclopentadienes were investigated as control experiments for the Grignard cycloadditions.



1 **2** **3**, X = H **4**, X = D

Of the wide variety of methods available for generation of benzyne,[1] only organoalkali and organomagnesium routes appeared likely to be compatible with the cyclopentadienyl anion. The reaction of 2-bromofluorobenzene with magnesium in THF (tetrahydrofuran) was chosen because of its previous success in cycloadditions of benzyne to cyclopentadienyl-[2,3] and indenylmagnesium bromide,[3,4] because of the ease of preparation and the ionic character of cyclopentadienyl Grignard reagents, and because of failure in preliminary experiments to produce cycloadducts from cyclopentadienyllithium, *o*-dihalobenzenes, and alkyllithiums.

Results

Diene Cycloadditions.—All additions to dienes were carried out by generating benzyne from 2-bromofluorobenzene and magnesium in a refluxing THF solution about 1 *M* in the diene. The benzonorbornadienes produced in 45–65% yields were isolated by distillation and/or glpc. Several side products were

(1) R. W. Hoffmann, "Dehydrobenzene and Cycloalkynes," Academic Press, New York, N. Y., 1967.

(2) G. Wittig and E. Knauss, *Chem. Ber.*, **91**, 895 (1958).

(3) W. T. Ford, R. Radue, and J. A. Walker, *Chem. Commun.*, 966 (1970).

(4) C. F. Huebner and E. M. Donoghue, *J. Org. Chem.*, **33**, 1678 (1968).

also isolated by glpc and identified by their spectral properties and melting points as biphenylene, triphenylene, 2-fluorobiphenyl, and unreacted 2-bromofluorobenzene. Normally reaction mixtures were hydrolyzed with saturated aqueous ammonium chloride. Deuterolysis of the mixture produced from cyclopentadiene and benzyne gave **3** containing 0.05 atom excess D, demonstrating that the initially formed 2-fluorophenylmagnesium bromide produced benzyne faster than it abstracted a proton from cyclopentadiene to produce **1**.

An equilibrium mixture of methyl-1,3-cyclopentadienes contained 44.5% 1-, 54.5% 2-, and <1% 5-methyl isomers by glpc at 27°.[5] Addition of a similar mixture to benzyne in refluxing THF (65–70°) produced the methylbenzonorbornadienes shown in Table I. Under these conditions the methylcyclopentadiene

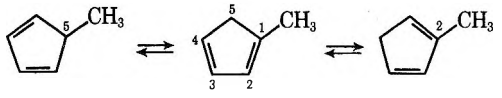
TABLE I

DISTRIBUTIONS OF METHYLBENZONORBORNADIENES PRODUCED BY ADDITION OF BENZYNE TO ISOMERIC METHYLCYCLOPENTADIENES AND TO METHYLCYCLOPENTADIENYLMAGNESIUM CHLORIDE

	% of mixture[a]		
Position of CH_3	From dienes	From Grignard	Statistical[b]
1	33	12	40
2	64	71	40
syn-9	3	17	10
anti-9	*c*	*c*	10
Yield,[d] %	45	21	

[a] Percentages measured by glpc and nmr may be considered accurate to ±2%. [b] Theoretical product distribution for nonselective addition of benzyne to Grignard and nonselective protonation at C_9 during hydrolysis. [c] Not detected by glpc or nmr; ≤1%. [d] Measured by glpc.

isomers interconverted by [1,5] sigmatropic hydrogen shifts with half-times of the same order of magnitude as the time over which benzyne was generated.[6]



An equilibrium mixture of the dimethylcyclopentadienes has been estimated to contain >90% 1,3, <5% 1,4, and <5% 2,5 isomers by uv and Raman spectroscopy at ambient temperature.[10] The pmr spectrum of the mixture used here showed no signal at higher field than δ 1.7. Therefore it contained ≤1% of the 2,5 isomer, but the relative amounts of 1,3 and 1,4 isomers were unknown. The distribution of dimethylbenzonorbornadienes formed by cycloaddition of this mixture[6] to benzyne is shown in Table II. Presumably the relative amounts of 1,3 and 1,4 isomers formed were not greatly different from the relative amounts of starting 1,3- and 1,4-dimethylcyclopentadiene. The product mixture contained much more of the 2,*syn*-

(5) S. McLean and P. Haynes, *Tetrahedron*, **21**, 2313 (1965).

(6) Half-times at 65° for conversions of 5- to 1-methylcyclopentadiene in CCl_4,[7] 1,5- to 1,2-dimethylcyclopentadiene neat,[8] and 5- to 1-trimethylsilylcyclopentadiene in benzene[9] were 1.15, 5.0, and 32 min, respectively. Benzyne generation times were 15–60 min.

(7) S. McLean, C. J. Webster, and R. J. D. Rutherford, *Can. J. Chem.*, **47**, 1555 (1969).

(8) S. McLean and P. Haynes, *Tetrahedron*, **21**, 2329 (1965).

(9) A. J. Ashe, *J. Amer. Chem. Soc.*, **92**, 1233 (1970).

(10) V. A. Mironov, E. V. Sobolev, and A. N. Elizarova, *Tetrahedron*, **19**, 1939 (1963).

TABLE II

DISTRIBUTIONS OF DIMETHYLBENZONORBORNADIENES PRODUCED BY ADDITION OF BENZYNE TO ISOMERIC DIMETHYLCYCLOPENTADIENES AND TO 1,3-DIMETHYLCYCLOPENTADIENYLMAGNESIUM CHLORIDE[a]

	% of mixture		
Positions of CH_3	From dienes	From Grignard	Statistical
1,3	82	26	40
1,4	13	3	20
2, *syn*-9	5	71	20
2, *anti*-9	*c*	*c*	20
Yield, %	59	32	

[a] See footnotes of Table I.

9-dimethyl isomer than the reactant mixture contained of 2,5-dimethylcyclopentadiene, indicating that benzyne reacted faster with 2,5- than with 1,3- and 1,4-dimethylcyclopentadienes.

An equilibrium mixture of trimethylsilylcyclopentadienes contained 3% 1-, 7% 2-, and 90% 5-substituted isomers by the integrated areas of the trimethylsilyl peaks in their pmr spectrum at 30°.[9] The mixture used in this work contained 4% 1-, 11% 2-, and 85% 5-trimethylsilylcyclopentadiene at 42° by the same method. Cycloaddition of the mixture[6] to benzyne at 65–70° produced the trimethylsilylbenzonorbornadienes shown in Table III.

TABLE III

DISTRIBUTIONS OF TRIMETHYLSILYLBENZONORBORNADIENES PRODUCED BY ADDITION OF BENZYNE TO ISOMERIC TRIMETHYLSILYLCYCLOPENTADIENES AND TO TRIMETHYLSILYLCYCLOPENTADIENYLMAGNESIUM CHLORIDE[a]

	% of mixture		
Position of $(CH_3)_3Si$	From dienes	From Grignard	Statistical
1	16	16	40
2	12	61	40
syn-9	2	21	10
anti-9	70	2	10
Yield, %	52	14	

[a] See footnotes of Table I.

An equilibrium mixture of *tert*-butylcyclopentadienes contained only the 1 and 2 isomers in 53:47 relative amounts according to their 220-MHz pmr spectrum at 22°, but it is not known which was the major isomer. Cycloaddition of the mixture[6] to benzyne at 65–70° produced the *tert*-butylbenzonorbornadienes shown in Table IV.

TABLE IV

DISTRIBUTIONS OF *tert*-BUTYLBENZONORBORNADIENES PRODUCED BY ADDITION OF BENZYNE TO ISOMERIC *tert*-BUTYLCYCLOPENTADIENES AND TO *tert*-BUTYLCYCLOPENTADIENYLMAGNESIUM CHLORIDE[a]

	% of mixture		
Position of $(CH_3)_3C$	From dienes	From Grignard	Statistical
1	33	10	40
2	67	90	40
syn-9	*c*	*c*	10
anti-9	*c*	*c*	10
Yield, %	57	29	

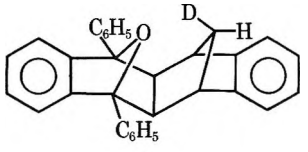
[a] See footnotes of Table I.

Grignard Cycloadditions.—Substituted cyclopentadienylmagnesium chlorides were prepared from ethylmagnesium chloride and the previously described diene mixtures. One additional side product, 2-ethylbi-

phenyl, formally derived from one molecule of excess ethylmagnesium chloride and two molecules of benzyne, was found in Grignard cycloadditions. No 2-fluorophenylcyclopentadiene (reported by Wittig and Knauss[2]) or other compound formed from any cyclopentadiene was found.

Incorporation of 0.90–0.98 atom of deuterium into product mixtures by deuterolysis proves that cycloadditions proceeded *via* the Grignard reagents **2** and **6a–c**. The product distributions obtained from methyl-, 1,3-dimethyl, trimethylsilyl-, and *tert*-butylcyclopentadienylmagnesium chlorides are shown in Tables I–IV and are compared to statistical distributions that would be obtained by nonselective cycloaddition of benzyne to cyclopentadienyl anions. The distributions of Grignard cycloadducts in Tables I–IV represent only deuterated products. All nondeuterated products were assumed to be formed by cycloaddition of benzyne to a trace of residual dienes. Two observations based on the product distributions for Grignard cycloadditions are clear. (1) Benzyne added selectively to substituted cyclopentadienylmagnesium chlorides, favoring placement of substituents at the 2 position of the benzonorbornadienes. (2) Most or all of the 9-substituents in the benzonorbornadienes were syn as a result of stereospecific protonation anti to the benzene ring during hydrolysis.

Structure Proof.—Stereospecific formation of **4** was proven by two pmr methods. (1) In **3** H_{9s} and H_{9a} gave an AB quartet, but in **4** only a single broad peak appeared at δ 2.12, the chemical shift of H_{9s} in **3**.[11] (2) By the method of Cristol and Noreen[13] the diphenylisobenzofuran adduct (**5**) of **4** had no detectable H_{9a},



5

and its H_{9s} signal appeared as a broad multiplet with no splitting >2 Hz. These results indicated $\leq 5\%$ D in position 9s and $\geq 95\%$ D in position 9a. The extent and position of deuteration were independent of the method of deuterolysis. Addition of D_2O to the reaction mixture, addition of the reaction mixture to D_2O, and addition of the reaction mixture to D_2O containing excess acetic acid-*O*-*d* dropwise with rapid stirring all incorporated 0.91–0.97 atom excess D. Therefore no hydrogen exchange took place after deuterolyses.

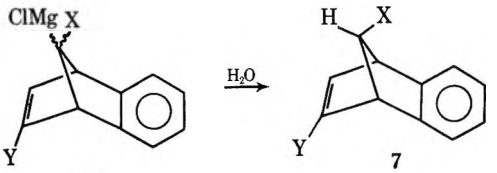
All of the gross structures of cycloadducts were determined by elemental analysis, mass spectra, and ir spectra. Some spectra were obtained with mixtures of two isomers because of inability to separate them by glpc. The mass spectra all had intense molecular ions, peaks due to loss of CH_3 and CH_2 groups, and peaks at *m/e* 141 ($C_{11}H_9^+$) and 115 ($C_9H_7^+$). Base peaks for the methyl- and dimethylbenzonorbornadienes arose from loss of CH_3. Base peaks for the trimethylsilyl compounds were *m/e* 73 [$(CH_3)_3Si^+$] and for the *tert*-butylbenzonorbornadienes were the molecular ion or *m/e* 141. The fragmentation patterns were very similar to those reported for other benzonorbornadiene derivatives.[12c] The ir spectra all had peaks at approximately 3060, 2960, 2925, 1450, and 1010 cm^{-1} and in the 890–690-cm^{-1} region in agreement with observations of other substituted benzonorbornadienes.[12d]

The substituted benzonorbornadienes were identified by their pmr spectra listed in Table V. Chemical shifts and coupling constants generally agreed with literature data for other benzonorbornadienes,[12] and integrated areas of spectral peaks also supported the assignments.

In all compounds unsubstituted at C_9 in which chemical shifts for H_{9a} and H_{9s} could be assigned, H_{9s} appeared at higher field as previously observed.[12] Long-range couplings between H_2, H_3, and H_{9s} were used to make the assignments. Coupling constants were determined by first-order analyses when possible. For compounds in which H_2 and H_3 were chemically equivalent, the vinyl region of the spectrum appeared as approximately a triplet, the AA′ portion of an AA′XX′ spectrum. In such cases just the sum $J_{1,2} + J_{1,3}$ could be determined.[12d] All couplings were verified by double irradiation experiments.

Configurations of compounds bearing the substituents listed in Table V or deuterium at C_9 were assigned by long-range coupling and by chemical analogy. The long-range coupling between H_2 and H_{9s} is well known in norbornenes and norbornadienes[12,14,15] as well as in benzonorbornadienes.[12] In this investigation the $J_{1,2}$ and $J_{1,3}$ values observed were ≤ 0.5 Hz but clearly discernible by decoupling experiments. No such couplings could be detected in compounds assigned as *syn*-9-substituted benzonorbornadienes.

In Grignard cycloadditions hydrolyses of all of the intermediate 9-substituted 9-benzonorbornadienylmagnesium chlorides (**6a–c**) produced *syn*-9-substituted benzonorbornadienes (**7a–c**). Moreover, deuterolyses of all 9-benzonorbornadienylmagnesium halides incorporated deuterium in the *anti*-9 position of the benzonorbornadiene, as evidenced by the lack of H_{9a} signals and the disappearance of $J_{9s,9a}$ in the H_{9s} signals in their pmr spectra. *anti*-9-Methylbenzonorbornadiene (**8**) was not produced by either diene or



6 **7**

a, X = CH_3; Y = H
b, X = CH_3; Y = CH_3
c, X = $Si(CH_3)_3$; Y = H

(11) The relative chemical shifts of H_{9s} and H_{9a} in **3** have been established by specific deuteration and by consistent long-range coupling between $H_{2,3}$ and H_{9s} in benzonorbornadiene derivatives.[12]

(12) (a) N. Inamoto, S. Masuda, K. Tori, K. Aono, and H. Tanida, *Can. J. Chem.*, **45**, 1185 (1967); (b) K. Tori, K. Aono, Y. Hata, R. Muneyuki, T. Tsuji, and H. Tanida, *Tetrahedron Lett.*, 9 (1966); (c) S. J. Cristol and G. W. Nachtigall, *J. Org. Chem.* **32**, 3738 (1967); (d) M. E. Brennan and M. A. Battiste, *ibid.*, **33**, 324 (1968).

(13) S. J. Cristol and A. L. Noreen, *J. Amer. Chem. Soc.*, **91**, 3969 (1969). I thank Dr. Cristol for supplying copies of their nmr spectra of **5**.

(14) (a) B. Franzus, W. C. Baird, Jr., N. F. Chamberlain, T. Hines, and E. I. Snyder, *ibid.*, **90**, 3721 (1968); (b) A. P. Marchand and J. E. Rose, *ibid.*, **90**, 3724 (1968); and references in these papers.

(15) (a) E. I. Snyder and B. Franzus, *ibid.*, **86**, 1166 (1964); (b) P. Laszlo and P. v. R. Schleyer, *ibid.*, **86**, 1171 (1964); (c) J. C. Davis, Jr., and T. V. Van Auken, *ibid.*, **87**, 3900 (1965); (d) N. H. Werstiuk, *Can. J. Chem.*, **48**, 2310 (1970).

TABLE V

PROTON MAGNETIC RESONANCE SPECTRA OF SUBSTITUTED BENZONORBORNADIENES

A. Chemical Shifts ($\delta_{CCl_4}^{TMS}$)[a]

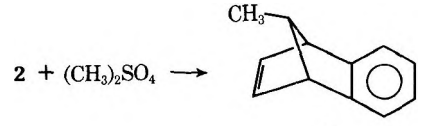
Substituents	Registry no.	H_1	H_4	H_2	H_3	H_{5-8}	H_{9s}[b]	H_{9a}[b]	CH_3
None[c]		3.76		6.66		6.7–7.2	2.15	2.18_5	
1-CH_3	31893-12-6		3.74	~6.7	6.38	6.7–7.2	AB 2.15		1.65
2-CH_3	31893-13-7	3.67	3.41		6.09	6.65–7.2	2.14_0	2.24_8	1.77
syn-9-CH_3	31893-14-8	3.45			6.6–7.4			~2.8	0.67
anti-9-CH_3	31893-15-9	3.50		6.49		6.7–7.3	2.74		1.03
1,3-$(CH_3)_2$	31893-16-0		3.38	5.82		6.75–7.2	2.09_2	2.22_8	1.59, 1.78
1,4-$(CH_3)_2$	31893-17-1			6.33		6.7–7.2	AB 2.12		1.58
2, *syn*-9-$(CH_3)_2$	31893-18-2	3.34	3.08		6.11	6.7–7.2		2.78	0.63, 1.77
1-$Si(CH_3)_3$	31862-26-7		3.82		6.7–7.5		AB 2.14		0.22
2-$Si(CH_3)_3$	31893-19-3	3.84_5, 3.90		6.93		6.7–7.1	2.14	2.14	0.03
syn-9-$Si(CH_3)_3$	31893-20-6	3.81		6.85		6.7–7.1		2.12	−0.38
anti-9-$Si(CH_3)_3$	31893-21-7	3.85		6.67		6.68–7.10	2.23		0.01
1-$C(CH_3)_3$	31893-22-8		3.71	6.63	6.71	6.7–7.3	2.16	2.22	1.24
2-$C(CH_3)_3$	31893-23-9	3.73			6.08	6.7–7.2	2.14	2.18	1.01

B. Coupling Constants ($|J|$, Hz)[d]

Substituents	1,2; 3,4	1,3; 2,4	1,9s; 1,9a; 4,9s; 4,9a[e]	2,9s; 3,9s	9s,9a	2,CH_3; 3,CH_3	9s,CH_3; 9a,CH_3
None[c]	Σ^f = 3.9		1.6	0.4	6.9		
2-CH_3	Σ^f = 3.4		1.6	0.4	6.7	1.8	
anti-9-CH_3	Σ^f = 3.8		1.8	0.5			6.5
1,3-$(CH_3)_2$	*g*	*g*	1.65	0.3	6.8	1.5	
2, *syn*-9-$(CH_3)_2$	*g*	*g*	1.5			1.7	6.7
1-$Si(CH_3)_3$	*g*	*g*	1.6	*g*	*g*		
2-$Si(CH_3)_3$	2.8	0.85	1.55	<0.3	*g*		
syn-9-$Si(CH_3)_3$	Σ^f = 3.7		1.25				
anti-9-$Si(CH_3)_3$	Σ^f = 3.9		1.5	0.4			
1-$C(CH_3)_3$	2.7	1.2	1.7	0.5, <0.3	6.8		
2-$C(CH_3)_3$	3.0	1.1	1.65	<0.3	*g*		

[a] Values are believed accurate to ±0.04 ppm unless otherwise indicated to be approximations. [b] Chemical shift differences between H_{9s} and H_{9a} are believed accurate to ±0.005 ppm. Values listed as AB denote the average chemical shift. [c] The chemical shifts reported are from this investigation. They are different from but agree favorably with previous reports.[12b,c] [d] J values were determined by first-order analysis to ±0.3 Hz, except for $J_{2,9s}$ ±0.1 Hz. [e] Average value of all such couplings. [f] $\Sigma = J_{1,2} + J_{1,3}$. NOTE ADDED IN PROOF.—The coupling patterns observed may be equally compatible with $J_{1,2} = 3.1$, $J_{1,3} = 0.9$, $J_{1,4} = 1.9$ Hz or similar values according to the analysis of W. B. Smith, S. Biesemeier, and D. L. Davenport, *J. Org. Chem.*, **36**, 2853 (1971), but the spectra available do not permit distinction between the $J_{1,4} = 0.0$ and $J_{1,4} = 1.9$ assignments. [g] Could not be determined from spectra available.

Grignard cycloaddition, but it was obtained by methylation of **2**. Both hydrolysis and methylation of the intermediates from Grignard cycloaddition gave stereospecific *anti*-9 capture of the incoming electrophile. The structural assignments in Table V have been based both on observations of $J_{2,9s}$ and on stereospecific capture of Grignard cycloadducts.



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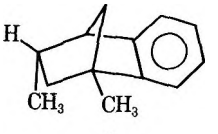
None of the structural assignments depend on relative chemical shifts of syn- and anti-9 substituents of isomeric benzonorbornadienes. However, in both methyl and trimethylsilyl compounds the syn-9 substituent appeared 0.36–0.39 ppm further upfield than the anti-9 substituent, as expected from location of the methyl groups in the shielding region of the aromatic ring current.

Hydrogenation of a mixture of dimethylbenzonorbornadienes and isolation by glpc gave samples of 1,-*endo*-3- and *endo*-2,*syn*-9-dimethylbenzonorbornenes (**9** and **10**). The easily identifiable aliphatic hydrogen peaks in the pmr spectrum of **9** were $\delta_{CCl_4}^{TMS}$ 0.52 (d, J = 6.8 Hz, 3 H, *endo*-3-CH_3), 1.50 (s, 3 H, 1-CH_3), 1.62 (AB q, 2 H, $H_{9a,9s}$), 2.8–3.0 (br d, J = 4.5–5.0 Hz, 1 H, H_4). The easily identifiable aliphatic hydrogen peaks in the pmr spectrum of **10** were $\delta_{CCl_4}^{TMS}$ 0.52 (d, J =



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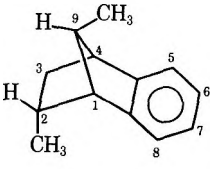

10

6.6 Hz, 3 H, *endo*-2-CH_3), 0.68 (d, J = 6.8 Hz, 3 H, *syn*-9-CH_3), 2.65–2.95 (m, 2 H, $H_{1,4}$). The peaks at 0.52 in **9** and **10** were assigned to *endo*-methyls because of their identical chemical shifts. The peak at δ 0.68 in **10** was assigned to syn-9-methyl because of its preparation by sterospecific exo hydrogenation, not because its position was unaffected by removal of the shielding anistropy of the C_2–C_3 double bond. (Hydrogenation of an *anti*-9-methyl compound presumably would proceed more slowly or with different stereoselectivity.) Similar chemical shift arguments 3 in the past have led to errors in assignments of the syn- and anti-9 hydrogens of **3**[12a] and the syn- and anti-7 hydrogens of norbornene.[14] Moreover, the chemical shifts of the methyl groups in *syn*- and *anti*-7-methyl-

norbornene are δ 0.70 and 0.79, respectively,[16] and both methyl groups in the *N*-phenylmaleimide adduct of 5,5-dimethylcyclopentadiene appear at δ 1.05.[5] All of these data indicate that chemical shifts must not be used to assign configuration at the bridge position in norbornenes, benzonorbornadienes, and related compounds.

Discussion

Diene Cycloadditions.—At 65–70° isomerizations of substituted cyclopentadienes by [1,5] sigmatropic hydrogen shifts competed with their cycloadditions to benzyne.[6] The detailed rate data for isomerization and cycloadditions needed to determine accurately relative rates of addition of the various methyl-, dimethyl-, *tert*-butyl-, and trimethylsilylcyclopentadienes to benzyne are not available, but, since the starting diene mixtures were either at or close to equilibrium during cycloaddition, the product distributions in Tables I, II, and IV indicate qualitatively the relative reactivities of the cyclopentadienes by position of alkyl substitution to be 2 > 1. No estimation of relative reactivity of 5-methyl- or 2,5-dimethyl-1,3-cyclopentadiene is warranted because of uncertainties in the relative yields of minor cycloadducts. A similar analysis of the equilibrium mixture of trimethylsilyl-1,3-cyclopentadienes and the distribution of their cycloadducts with benzyne indicates their relative reactivities by position of substitution to be 1 > 2 > 5. The lesser reactivity of 5-trimethylsilyl-1,3-cyclopentadiene can be explained by steric hindrance to addition of benzyne to its *syn*-trimethylsilyl face. The greater reactivity of 1- than of 2-trimethylsilyl-1,3-cyclopentadiene may be due to the greater polarity of the former, expected from the slightly electron-withdrawing resonance effect ($\sigma_m = -0.121$, $\sigma_p = -0.072$)[17] of the trimethylsilyl group.

The preferred mode of addition of benzyne to 5-methyl- and 2,5-dimethyl-1,3-cyclopentadiene placed the 9-methyl groups in the benzonorbornadienes syn to the benzene ring. In other Diels–Alder reactions of 5-methyl-1,3-cyclopentadiene, *N*-phenylmaleimide added endo to form syn and anti bridge methyl compounds in about equal amounts,[5] and maleic anhydride formed a 12:1 mixture of isolated endo adducts in which the major product was presumed to have the bridge methyl group syn to the norbornene double bond (anti to the incoming dienophile)[18] because of the abnormally slow addition of 5,5-dimethyl-1,3-cyclopentadiene to maleic anhydride.[19] However, the latter and other[20] stereochemical assignments based on chemical shifts of bridge protons or bridge methyl groups in Diels–Alder adducts of 5-methylcyclopentadienes must be considered questionable because of the more recently demonstrated unreliability of such chemical shift arguments.[5,15] Cycloadditions of common dienophiles to other 5-substituted 1,3-cyclopentadienes have given both syn and anti adducts.[21]

The preferred *syn*-9-methyl orientation in benzyne adducts of 5-methyl-1,3-cyclopentadienes can be explained by attractive van der Waals forces between the methyl group and benzyne. The optimum overlap of the reactive orbitals of benzyne and the π bonds of a cyclopentadiene places the planes of the reactants nearly perpendicular to each other in the transition state for cycloaddition, minimizing steric hindrance with a 5 substituent on cyclopentadiene. Attractive interaction between the bridge methyl group and the incipient dienophile has been offered to explain the slow rate of retro Diels–Alder fragmentation of 1,7,7-trimethylbicyclo[2.2.1]heptene compared to that of bicyclo[2.2.1]heptene.[22] Preferred endo orientations of methyl groups in the Diels–Alder adducts of cyclopentadiene and methyl-substituted acrylic acids, esters, and nitriles have been explained both by attraction of the methyl groups of the dienophiles to the C_3–C_4 bond of cyclopentadiene and by steric hindrance between methyl groups and the 5 hydrogen of cyclopentadiene in the transition state for cycloaddition.[23] Similar explanations have been offered for the prevailing endo orientation of addition of cyclopentene,[24] norbornene,[25] cyclopropene,[26] and propene[27] to cyclopentadiene.[28] In contrast, analogs of cyclopentadiene which have lone pair or π-bonded electrons at the 5 position gave nearly equal mixtures of exo and endo adducts with cycloalkene dienophiles, as in the additions of cyclopropene to furan[29] and cyclopentene to tetraphenylcyclopentadienone.[30]

Grignard Cycloadditions.—Cyclopentadienyl Grignard reagents in THF consist of planar, aromatic cyclopentadienide ions associated with magnesium and halide ions according to their ir and uv spectra.[31] The extent of aggregation at high concentrations in THF is not known, but analogy to a wide variety of ionic organoalkali compounds suggests that they are ion pairs or higher aggregates.[32] The low conductivities of alkali cyclopentadienides and magnesium cyclopentadienide in THF also support aggregation.[33]

The high reactivity of benzyne has resulted in its capture by [2 + 2], [3 + 2], and [4 + 2] cycloaddi-

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(24) (a) P. Wilder, Jr., C. F. Culberson, and G. T. Youngblood, *ibid.*, **81**, 655 (1959); (b) S. J. Cristol, W. K. Seifert, and S. B. Soloway, *ibid.*, **82**, 2351 (1960).
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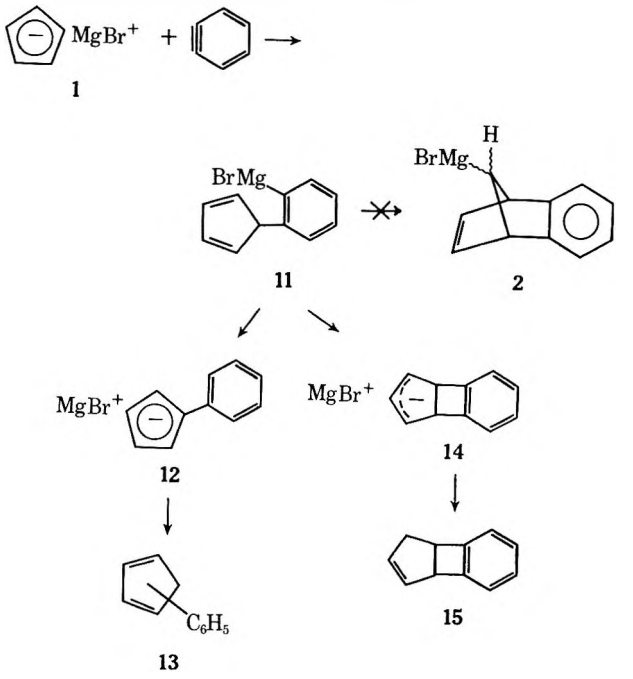
(26) K. B. Wiberg and W. J. Bartley, *ibid.*, **82**, 6375 (1960).
(27) N. A. Belikova, V. G. Berezkin, and A. F. Platé, *Zh. Obshch. Khim.*, **32**, 2942 (1962).
(28) For reviews see (a) J. Sauer, *Angew. Chem., Int. Ed. Engl.*, **6**, 16 (1967); (b) J. G. Martin and R. K. Hill, *Chem. Rev.*, **61**, 537 (1961); (c) A. Wasserman, "Diels–Alder Reactions," Elsevier, Amsterdam, 1965.
(29) R. W. LaRochelle and B. M. Trost, *Chem. Commun.*, 1353 (1970).
(30) K. N. Houk, *Tetrahedron Lett.*, 2621 (1970).
(31) W. T. Ford, *J. Organometal. Chem.*, **32**, 27 (1971).
(32) For extensive reviews see (a) M. Szwarc, "Carbanions, Living Polymers, and Electron-Transfer Processes," Interscience, New York, N. Y., 1968, Chapters V and VI; (b) J. F. Garst in "Solute–Solvent Interactions," J. F. Coetzee and C. D. Ritchie, Ed., Marcel Dekker, New York, N. Y., 1969, pp 539–605.
(33) W. Strohmeier, H. Landsfeld, and F. Gernert, *Z. Elektrochem.*, **66**, 823 (1962).

tions,[34] ene reactions, and nucleophilic additions.[1] An [8 + 2] cycloaddition of benzyne to a heptafulvene was reported recently.[36] In many instances nucleophilic addition and cycloaddition to benzyne proceeded at similar rates, particularly when an organometallic route to benzyne was used. The triphenylene, biphenylene, 2-fluorobiphenyl, and 2-ethylbiphenyl found as side products in the present investigation indicate that nucleophilic additions of 2-fluorophenylmagnesium bromide, 2′-fluoro-2-biphenylylmagnesium bromide, and ethylmagnesium bromide to benzyne and cycloadditions of cylopentadienes and cyclopentadienylmagnesium bromides to benzyne all proceeded at similar rates. No product explicable by stepwise nucleophilic addition of cyclopentadienylmagnesium bromide (or chloride) to benzyne was isolated. The products expected from such an addition would be either phenylcyclopentadiene (**13**) or 6,7-benzobicyclo-[3.2.0]hepta-2,6-diene (**15**) as shown in Scheme I.

SCHEME I

EXPECTED COURSES OF STEPWISE ADDITION OF CYCLOPENTADIENYLMAGNESIUM BROMIDE TO BENZYNE



Conversion of the intermediate 2-(5-cyclopenta-1,3-dienyl)phenylmagnesium bromide (**11**) to the known intermediate 2 is highly unlikely because it would require Grignard addition to the 2 position of a 1,3 diene and convert a more stable aryl Grignard reagent to a less stable secondary alkyl Grignard reagent. For similar reasons there is no likely path for rearrangement of **12** or **14** to **2**.

The simplest mechanism which accounts for intermediate Grignards **2**, **6a–c**, and isomers of **6a–c** is [3 + 2] cycloaddition[34] of benzyne to cyclopentadienyl anions, which may also be called $\pi^4s + \pi^2s$ cycloaddition.[37] This mode of cycloaddition is predicted theoretically to be concerted.[37] Benzyne is thought to be a ground-state singlet on the basis of theory[38] and experiments which have demonstrated that it adds stereospecifically [4 + 2] to isomeric 2,4-hexadienes[39,40] and *trans,trans*-dimethyl muconate[39] and nonspecifically [2 + 2] to the isomeric 1,2-dichloroethylenes,[39] isomeric propenyl ethers,[41] and *trans*-cyclooctene.[42] It is well known that benzyne[43] and tetrahalobenzynes[44] are reactive enough to destroy the aromaticity of a benzene ring by cycloaddition. Reaction of tetrafluorobenzyne and nickelocene gave two 1:1 adducts, one of which was postulated to be formed *via* [3 + 2] cycloaddition.[45]

Methyl-, 1,3-dimethyl-, *tert*-butyl-, and trimethylsilylcyclopentadienylmagnesium chloride were added to benzyne in order to characterize better the transition states of these anionic cycloadditions. Benzyne's instability makes its reactions exothermic and accounts for its ability to convert relatively stable aromatic cyclopentadienyl Grignards to much less stable secondary alkyl Grignards. It follows that the transition state should more nearly resemble starting materials than products.[46] If product stability were important, the ease of formation of 9-substituted benzonorbornadienyl Grignard reagents would be $Si(CH_3)_3 > H > CH_3 > C(CH_3)_3$ because of the relative abilities of these groups to stabilize adjacent carbanions.[47] The product distributions for addition of benzyne to each cyclopentadienyl Grignard reagent (Tables I–IV) show no correlation with the expected relative stabilities of substituted 9-benzonorbornadienyl Grignard reagents.

If substituents were to perturb the charge density within a cyclopentadienide ion, the positions of highest charge density would be expected to react most readily with electrophilic benzyne. Methylation of the methylcyclopentadienyl anion was found by McLean and Haynes[5] to produce a 3.5:1.0:0.2 distribution of 1,5-:2,-5-:5,5-dimethylcyclopentadienes. Their product distribution was rationalized with a Hückel molecular orbital calculation which gave the π-electron densities at the 1, 2, and 3 positions of the anion as 1.01, 1.28, and 1.22, respectively. In contrast, ^{13}C nmr chemical

(34) This nomenclature refers to the number of atoms in each addend which become part of the new ring of the adduct.[35]

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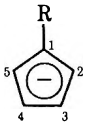
(46) G. S. Hammond, *J. Amer. Chem. Soc.*, **77**, 334 (1955).

(47) (a) D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press, New York, N. Y., 1965, Chapter II; (b) D. J. Peterson, *J. Organometal. Chem.*, **9**, 373 (1967); (c) G. A. Gornowicz and R. West, *J. Amer. Chem. Soc.*, **90**, 4478 (1968); (d) A. E. Bey and D. R. Weyenberg, *J. Org. Chem.*, **31**, 2036 (1966); (e) F. Jaffe, *J. Organometal. Chem.*, **23**, 53 (1970).

shifts of the ring carbon atoms in methyl- and 1,3-dimethylcyclopentadienylmagnesium chloride in THF indicate nearly equal π-electron densities at all ring positions,[48] in disagreement with the HMO results. The HMO calculation predicts the major cycloadduct of methylcyclopentadienylmagnesium chloride and benzyne to be a 9-methyl isomer, while the ^{13}C chemical shifts predict nearly statistical distribution of cycloadducts. The anion-stabilizing ability of silicon should increase electron density at the α carbon in trimethylsilylcyclopentadienylmagnesium chloride, an hypothesis supported by the ^{13}C chemical shifts of its ring carbon atoms.[48] This unequal charge distribution leads to the prediction that its major cycloadduct to benzyne would be 1-trimethylsilylbenzonorbornadiene. The data in Tables I–IV clearly indicate no correlation between either HMO or ^{13}C chemical shift estimates of charge distribution in substituted cyclopentadienyl Grignard reagents and the substituent orientations in their benzyne adducts.

Nevertheless, methylation of and benzyne addition to the methylcyclopentadienyl anion (**16a**) both preferred formation of a new carbon–carbon bond at the 2 position. Although it is unlikely that the benzyne addition proceeded stepwise, one new bond could be more nearly formed in the transition state than the second. The substituent orientations of benzyne adducts of the methyl-, 1,3-dimethyl-, and trimethylsilylcyclopentadienylmagnesium chloride additions are compatible with control of orientation of the earlier formed bond by the same factors which orient methylation of methylcyclopentadienyl anion at positions $2 > 3 > 1$, and control of orientation of the later formed bond at positions $3(4) > 2(5) > 1$ by steric effects. Thus formation of the first bond at C_2 would make C_4



16a, R = CH_3
b, R = $C(CH_3)_3$

and C_5 available for the second bond, with C_4 favored for steric reasons. The lack of a 9-*tert*-butylbenzonorbornadiene product from benzyne addition to *tert*-butylcyclopentadienylmagnesium chloride may be explained by steric hindrance to formation of the first new bond at C_2 in **16b**. Formation of the first bond at C_3 would make C_1 and C_5 available for the second bond with C_5 favored. Generally greater steric influence should be expected on formation of the second bond because at that time the addends are held together more tightly.

This discussion points out the similarities between alkylation of and benzyne addition to methylcyclopentadienide but unfortunately does not explain the preferred orientation of reactions at the 2 position. Mechanisms involving cationic or radical intermediates can also be devised for these cycloadditions, but they seem intuitively less likely in view of the carbanionic nature of cyclopentadienyl Grignard reagents. However, the intermediacy of benzonorbornadienyl Grignards 2 and **6a–c** and of isomers of **6a–c** is firmly established by deuteration.

(48) J. B. Grutzner and W. T. Ford, unpublished observations.

Experimental Section

General.—Microanalyses were performed by J. Nemeth and associates. Infrared spectra were obtained as thin films between sodium chloride plates on a Perkin-Elmer 521 instrument. Mass spectra were obtained on a Varian-MAT CH-5 instrument by J. Wrona. Deuterium analyses of the molecular ions were performed at low ionizing voltage to minimize fragmentation. Nmr spectra were obtained at ambient temperature in carbon tetrachloride on Varian T-60, A-60-A, HA-100, and HR-220 instruments. The HA-100 equipped with a Varian V-4315 frequency counter and a Hewlett-Packard Model 200ABR audio oscillator was used for chemical shift measurements and decoupling experiments.

Materials.—Tetrahydrofuran was distilled from calcium hydride just before use. 2-Bromofluorobenzene (Aldrich), deuterium oxide, 99.5% (Columbia), acetic acid-*O-d*, 99.5% (Aldrich), magnesium turnings (Baker), diphenylisobenzofuran (Aldrich), and ethylmagnesium chloride, 3.0 *M* in THF (Alpha) were used as obtained. Cyclopentadiene and methylcyclopentadiene were obtained from their dimers (Aldrich) by distillation and stored at −78° until use. The mixture of trimethylsilylcyclopentadienes was prepared from cyclopentadienyl sodium and freshly distilled chlorotrimethylsilane in THF.[49] The mixture of *tert*-butylcyclopentadienes was prepared from cyclopentadienylmagnesium bromide and freshly distilled 2-chloro-2-methylpropane in diethyl ether.[50]

1,3- and 1,4-dimethylcyclopentadienes were obtained as a mixture from 3-methyl-2-cyclopentenone (Aldrich) and methylmagnesium bromide by the method of McLean and Haynes.[5] In my hands dehydration of the intermediate 1,3-dimethyl-2-cyclopentanol occurred spontaneously during work-up. The dimethylcyclopentadienes were collected in a Dry Ice trap during removal of ether with a rotary evaporator and were redistilled, bp 85–97° (760 mm) (lit.[5] for pure 1,3-dimethylcyclopentadiene, 93–95°).

Analytical and Preparative Glpc.—Some analyses were performed with 0.125-in. columns on a Hewlett-Packard Model 700 instrument with thermal conductivity detector, and other analyses and all preparative separations were performed wih 0.25-in. columns on a Varian Model A-90-P instrument. The following columns were used: (A) 6 ft × 0.125 in. 10% UCW-98 on 80/100 Diataport S; (B) 20 ft × 0.125 in. 10% diethylene glycol succinate on 60/80 Chromosorb G; (C) 6 ft × 0.25 in. 20% Apiezon L on 60/80 Chromosorb W; (D) 10 ft × 0.25 in. 20% Apeizon L on 60/80 Chromosorb W; (E) 6 ft × 0.25 in. 20% SE-30 on 60/80 Chromosorb W. Isomeric compounds were assumed to have equal thermal conductivities. Compounds were proven stable under the glpc isolation conditions by lack of isomerization upon reinjection of pure isomers.

Diene Cycloadditions.—By the general method of Wittig and Knauss[2] an equimolar amount of 2-bromofluorobenzene in twice its volume of THF was added dropwise with stirring under nitrogen over 15–60 min to a 1 *M* solution of diene(s) in THF refluxing over 1 equiv of magnesium. After cooling to 25° the mixture was hydrolyzed with stirring by dropwise addition of saturated aqueous ammonium chloride or of deuterium oxide followed by ammonium chloride. The THF solution was separated. The aqueous residue was washed twice with diethyl ether, and the combined organic solution was dried and evaporated. Cycloadducts were isolated by distillation and/or glpc of the remaining yellow liquid.

Grignard Cycloadditions. General Procedure.—A 1 *M* solution of the cyclopentadienylmagnesium chloride was prepared by refluxing a THF solution of the diene and a 5–10% excess of ethylmagnesium chloride under nitrogen until the vinyl hydrogen nmr signals of the diene were completely replaced by ring hydrogen signals of the cyclopentadienyl Grignard. Generation of benzyne from an equimolar amount of 2-bromofluorobenzene,

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hydrolysis, and isolation of products were carried out by the method used in diene cycloadditions.

Benzonorbornadiene-*anti*-9-*d* (4). A.—On a 36-mmol scale, cyclopentadiene was converted to cyclopentadienylmagnesium bromide (pmr δ 5.96, s) in 2.5 hr. Deuterolysis was carried out by dropwise addition of D_2O to the Grignard mixture. Distillation through a 15-cm Vigreaux column gave crude **4**, bp 83–89° (13 mm) [lit.[2] bp 82.5–83° (12 mm)], 1.5 g (29%). By pmr **4** was contaminated with 15% of dicyclopentadiene and 2-ethylbiphenyl. Comparison of the areas of its proton signals at δ 3.76 and 2.12 indicated 0.90 atom excess D at the 9 position. Glpc on column E at 200° gave **4** >99.5% pure by analysis on column A at 185°. It contained 0.915 atom excess D by mass spectrometry.

B.—On a 19-mmol scale the final Grignard mixture was added by syringe to 2.5 ml of D_2O. A white gel formed during addition. Glpc on column C at 150° gave **4** which contained 0.97 atom excess D by pmr.

C.—On a 10-mmol scale the Grignard mixture was added dropwise by syringe to a rapidly stirred solution of 2.0 ml acetic acid-*O*-*d* and 5.0 ml D_2O. Glpc on column D at 165° gave **4** which contained 0.97 atom excess D by pmr.

The **diphenylisobenzofuran adduct of 4 (5)** was prepared according to Cristol and Noreen[13] in 54–61% yield after one crystallization from chloroform–ethanol, mp 252–254° (uncorrected). The adduct from A contained 0.907 atom excess D by mass spectrometry and adducts from A and C contained no trace of *anti*-9 hydrogen by 100-MHz pmr.

Addition of benzyne to methylcyclopentadienes on a 20-mmol scale gave methylbenzonorbornadienes in 45% yield (by glpc comparison to biphenyl standard on column C). Glpc on column C at 150° separated three isomers with retention times of 13.0, 15.5, and 18.0 min and relative areas (column A, 130°) of 3:35:62. A pmr spectrum of the mixture had methyl signals with relative areas 3:31:66 corresponding to the *syn*-9-, 1-, and 2-methyl compounds.

Anal. (of the isomeric mixture). Calcd for $C_{12}H_{12}$: C, 92.26; H, 7.74. Found: C, 92.15; H, 7.77.

1-Methylbenzonorbornadiene and 2-methylbenzonorbornadiene as isolated were each >95% pure by glpc on column C and identified by their ir, mass, and pmr spectra.

syn-**9-Methylbenzonorbornadiene** (7a) as isolated contained 25% of its 1-methyl isomer. It was identified in the mixture by its pmr spectrum.

anti-**9-Methylbenzonorbornadiene (8)** was prepared on a 20-mmol scale by adding dropwise at 25° the final Grignard mixture from cycloaddition of benzyne and cyclopentadienylmagnesium chloride to 7 ml of freshly distilled dimethyl sulfate. After stirring for 30 min the mixture was extracted with water and diethyl ether. The ether solution was washed three times with *M* sodium hydroxide and once with saturated sodium chloride, dried, and evaporated to a black oil. Chromatography over silica gel with petroleum ether (bp 30–60°) as eluent gave a brown oil which contained a 90:10 mixture of **3**:**8** by glpc on column A. The mixture was separated with column C at 155° and the components were identified by their pmr spectra. The yield of **8** was $\leq$3% by comparison to **3**.

Addition of benzyne to methylcyclopentadienylmagnesium chloride was followed by deuterolysis on a 20-mmol scale. Generation of methylcyclopentadienylmagnesium chloride (pmr δ 5.73, AA'BB') required 12 hr. The product mixture was analyzed by methyl peak areas in its pmr spectrum and by glpc on column C at 150° to contain 18% by glpc (16% by pmr) *syn*-9-methyl-, 13% (11%) 1-methyl-, and 69% (73%) 2-methylbenzonorbornadiene. Overall yield by glpc was 21%.

2-Methylbenzonorbornadiene-*anti*-9-*d* was isolated >95% pure by glpc on column C and identified by pmr, ir, and mass spectra. Its pmr spectrum was identical with that in Table V except that H_{9s} appeared as a single broad band at δ 2.14, H_{9a} was absent, and H_1 and H_4 were narrower. It contained 0.949 atom excess D by mass spectrometry.

Addition of Benzyne to 1,3- and 1,4-Dimethylcyclopentadiene. A.—On a 1.0-mmol scale the product mixture contained 81% 1,3-, 14% 1,4-, and 5% 2, *syn*-9-dimethylbenzonorbornadiene by pmr comparison of methyl peaks. By glpc on column C at 175° the yield was 59% of two components with retention times and relative areas of 10.0 (18%) and 12.2 min (82%). Collection from column C and identification by pmr showed that the first was a mixture of 1,4- and 2,*syn*-9 isomers and the second was the 1,3 isomer.

B.—On a 45-mmol scale benzyne was added to a mixture of ~70% 1,3-dimethylcyclopentadienylmagnesium chloride and ~30% dimethylcyclopentadienes (composition determined by pmr). Cycloadducts were isolated by distillation, bp 90–103° (9 mm), in 48% yield. The distillate was purified and analyzed by glpc on column C to contain 59% 1,4- and 2,*syn*-9- and 41% 1,3-dimethylbenzonorbornadiene.

Anal. (of the isomeric mixture). Calcd for $C_{13}H_{14}$: C, 91.71; H, 8.29. Found: C, 91.52; H, 8.34.

1,3-Dimethylbenzonorbornadiene was isolated from B >95% pure by glpc on column C and identified by its pmr, ir, and mass spectra.

2,*syn*-9-Dimethylbenzonorbornadiene (7b) was isolated from B contaminated with 8% 1,3 and 9% 1,4 isomer by pmr. It was identified by its pmr, ir, and mass spectra.

1,4-Dimethylbenzonorbornadiene was obtained from B as 23% of a mixture which contained 77% 2,*syn*-9 isomer and identified by its pmr spectrum.

Addition of benzyne to 1,3-dimethylcyclopentadienylmagnesium chloride on a 20-mmol scale gave a 32% yield (glpc on column C at 160°) of dimethylbenzonorbornadienes after deuterolysis. Generation of the Grignard (pmr δ 5.46, s; 2.02, s) required 60 hr for 97.5% conversion. The product mixture was purified with column C and analyzed with column B to contain 69% 2,*syn*-9- and 1,4- and 31% 1,3-dimethylbenzonorbornadiene. The product distribution from Grignard in Table II includes deuterated products only.

1,3-Dimethylbenzonorbornadiene-*anti*-9-*d* as isolated was >95% pure by column C and identified by pmr, ir, and mass spectra. Its pmr spectrum was identical with that in Table V except that H_{9s} was broad, H_{9a} was missing, and H_4 was narrowed. It contained 0.812 atom excess D by mass spectrometry, indicating that part of its was formed from 1,3-dimethyl-1,3-cyclopentadiene instead of 1,3-dimethylcyclopentadienylmagnesium chloride.

2,*syn*-9-Dimethylbenzonorbornadiene-*anti*-9-*d* was isolated with column C and identified by ir, mass, and pmr spectra. It contained 10% of its 1,4 isomer by pmr, which showed 9-CH_3 as a singlet, no trace of H_{9a}, and H_1 and H_4 narrower than reported in Table V. By mass spectrometry it contained 0.987 atom excess D, indicating that virtually all of it was formed from 1,3-dimethylcyclopentadienylmagnesium chloride.

Hydrogenation of dimethylbenzonorbornadienes by the sodium borohydride–chloroplatinic acid method of Brown and Brown[51] was performed with 0.6 mmol of mixture B. Products with retention times of 11.2 and 12.8 min were separated with column C at 140° and identified as *endo*-2,*syn*-9- and 1,*endo*-3-dimethylbenzonorbornene (**9** and **10**, respectively) by their pmr spectra (see Results). Relative yields were 56 and 44% and the overall yield was 21% by glpc on column B.

Addition of benzyne to trimethylsilylcyclopentadienes on a 20-mmol scale gave a 52% yield by glpc of trimethylsilylbenzonorbornadienes. Separation and analysis with column D at 220° gave 17% 1- (retention time 13.1 min), 15% 2- and *syn*-9- (17.2 min), and 68% *anti*-9-trimethylsilyl (19.6 min) isomers. Analysis of the mixture by areas of trimethylsilyl peaks in its pmr spectrum indicated 16% 1, 11% 2, 2% *syn*-9, and 71% *anti*-9 isomers.

Addition of Benzyne to Trimethylsilylcyclopentadienylmagnesium Chloride. A.—On a 20-mmol scale a 14% yield of trimethylsilylbenzonorbornadiene was found by glpc on column D. Generation of the Grignard reagent (pmr δ 0.12, s, 9 H; 6.13, AA'BB', 4 H) required 10 hr. The mixture was purified with column D and analyzed by pmr to contain 14% 1-, 58% 2-, 18% *syn*-9, and 10% *anti*-9-trimethylsilyl isomers. The deuterolysis of run B indicated that part of these products must have come from trimethylsilylcyclopentadiene, not from the Grignard reagent.

Anal. (of the mixture). Calcd for $C_{14}H_{18}Si$: C, 78.44; H, 8.46. Found: C, 78.59; H, 8.36.

B.—A mixture of 71% trimethylsilylcyclopentadienylmagnesium chloride and 29% trimethylsilylcyclopentadiene isomers (determined by pmr) was prepared from 19.6 mmol of trimethylsilylcyclopentadiene and 14 mmol of ethylmagnesium chloride. Addition of benzyne and deuterolysis gave a 27% yield of trimethylsilylbenzonorbornadienes by glpc on column D. Analysis and separation on column D gave 16% 1, 57% 2 and *syn*-9, and

(51) H. C. Brown and C. A. Brown, *J. Amer. Chem. Soc.*, **84**, 1493, 1494, 1495 (1962).

27% *anti*-9 isomers. By mass spectrometry these fractions contained 0.649, 0.947, and 0.046 atom excess D, respectively. By pmr the two compound mixture contained 73% 2 and 27% *syn*-9 isomers. The product distribution in Table III was calculated by assuming that only deuterated material was formed from the Grignard reagent.

1-Trimethylsilylbenzonorbornadiene was isolated from the preceding mixture (A) >95% pure and identified by its pmr, ir, and mass spectra.

2- and *syn*-9-trimethylsilylbenzonorbornadiene were isolated from mixture A as a 77:23 mixture (by pmr) and identified by their pmr, ir, and mass spectra.

***anti*-9-Trimethylsilylbenzonorbornadiene** was isolated from the diene cycloaddition >95% pure and identified by its pmr, ir, and mass spectra.

1-trimethylsilylbenzonorbornadiene-*anti*-9-*d* was isolated from mixture B and identified by its pmr spectrum, which showed a reduction in area and broadening of the $H_{9a,9s}$ signal but no other change from the data given in Table V. It contained 0.649 atom excess D by mass spectrometry. The *anti*-9-*d* configuration was assumed by analogy to other examples in this paper.

2- and *syn*-9-trimethylsilylbenzonorbornadiene-*anti*-9-*d* were isolated as a 73:27 mixture from run B and were identified by their combined pmr spectra, which were identical with those presented in Table V except for a slightly narrower H_1, H_4, multiplet and an H_{9a}, H_{9s} singlet equivalent to 0.75 H. The mixture contained 0.947 atom excess D by mass spectrometry. The *anti*-9-*d* configuration in the 2 isomer was assumed by analogy to previous examples.

Addition of benzyne to *tert*-butylcyclopentadienes on a 4.7-mmol scale gave a 57% yield by glpc of *tert*-butylbenzonorbornadienes. Separation and analysis with column D at 225° gave 33% 1 (retention time 21 min) and 67% 2 (15 min) isomers. Analysis of the mixture prior to glpc by areas of *tert*-butyl peaks in its pmr spectrum indicated 34% 1 and 66% 2 isomers.

Anal. (of the isomeric mixture). Calcd for $C_{15}H_{18}$: C, 90.85; H, 9.15. Found: C, 90.74; H, 8.89.

1- and 2-*tert*-butylbenzonorbornadiene as isolated by glpc were each >95% pure and were identified by their pmr, ir, and mass spectra.

Addition of Benzyne to *tert*-Butylcyclopentadienylmagnesium Chloride.—On a 19-mmol scale the Grignard reagent (pmr δ 1.20, s, 9 H; 5.79, AA'BB', 4 H) was generated in 12 hr. After deuterolysis a yield of 29% *tert*-butylbenzonorbornadiene was found by glpc. Analysis and separation on column D gave 12% 1 and 88% 2 isomers which contained 0.724 and 0.898 atom excess D, respectively. The product distribution in Table IV was calculated by assuming that the distribution of deuterated material was identical with that formed *via* Grignard.

1-*tert*-Butylbenzonorbornadiene-*anti*-9-*d* was isolated >95% pure and identified by its pmr, ir, and mass spectra.

2-*tert*-Butylbenzonorbornadiene-*anti*-9-*d* was isolated >95% pure and identified by its pmr, ir, and mass spectra. Its pmr spectrum showed a broad peak at δ 2.14 for H_{9s} and a much weaker half of an AB spectrum for residual H_{9a} compared to its undeuterated analog.

Registry No.—**4**, 31893-09-1; **9**, 31893-10-4; **10**, 31893-11-5; benzyne, 462-80-6.

Acknowledgments.—I thank the donors of the Petroleum Research Fund of the American Chemical Society for the support of Grant 1351-G1 and Robert Thrift and associates for extensive technical help with the nmr decoupling experiments.

Pseudo π Bonding in Saturated Hydrocarbons

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Received February 23, 1971

INDO MO calculations on a number of geometries of ethane lead us to conclude that the fraction of s character in the C–C "single" bond is directly proportional to the pseudo π bond order between the two atoms. This and previous results suggest that the length of the C–C "single" bond may be determined primarily by the π bond order.

The question as to the extent to which the carbon–carbon bond length depends upon π bond order or upon the hybridization in the σ bond has been the subject of considerable debate for several years.[2-6] Many studies have involved attempts to define appropriate models for single bonds resulting from the overlap of different types of hybrid atomic orbitals (sp^n, different n) in unsaturated and strained saturated hydrocarbons.

Maksić and Randić[6] recently examined a number of saturated hydrocarbons, for which the structures are accurately known, and used the method of maximum overlap[7] to calculate the hybridization of the atomic orbitals involved in the various bonds. These authors found a close correlation between the experimental bond lengths and the amount of s character calculated for the hybrid orbitals forming the single bonds. Miyazaki,[5] however, pointed out one of the dangers in using the localized bond approximation particularly for hybrid orbitals with little s character and came to the surprising conclusions that by neglecting the π overlap in ethylene and acetylene the calculated equilibrium bond lengths were essentially identical with those calculated for ethane. This would imply that π overlap is entirely responsible for the shortening of the carbon–carbon bond in the former two molecules. The question therefore arises: *If* bond lengths *are* essentially independent of the hybridization in the σ bond, how does one explain the correlations of Maksić and Randić[6] which were obtained for a large number of *saturated* hydrocarbons?

Because of the many difficulties inherent in experimental approaches to this question, we considered it highly desirable to examine the problem from a theoretical point of view. The INDO[8] approximate SCF MO method which has now been adequately tested and has been shown to give reliable results appeared to us to be most appropriate for this purpose. In this communi-

(1) National Science Foundation Undergraduate Research Participant, summer 1970. Acknowledgment is also made to the donors of The Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research.

(2) For a recent, concise review of the status of this controversy, see R. A. Alden, J. Kraut, and T. G. Traylor, *J. Amer. Chem. Soc.*, **90**, 74 (1968), and references cited therein.

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(6) Z. B. Maksić and M. Randić, *J. Amer. Chem. Soc.*, **92**, 424 (1970).

(7) L. Klasinc, Z. Maksić, and M. Randić, *J. Chem. Soc. A*, 755 (1966).

(8) J. A. Pople, D. L. Beveridge, and P. A. Dobosh, *J. Chem. Phys.*, **47**, 2026 (1967).

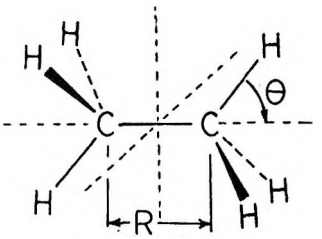

Figure 1.—The orientation of the reference ethane molecule in the Cartesian framework and the definition of R and θ.

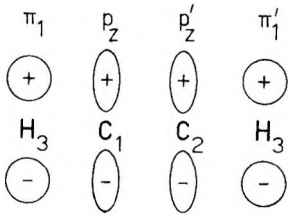

Figure 2.—The basis set of orbitals in ethane antisymmetric with respect to the XY plane.

cation we use the INDO method to show that both the above sets of data are compatible with the predominant effect on bond length being due to π bonding, and we describe a pseudo π bonding phenomenon which should be of general importance in studies involving strained σ systems.

For simplicity, we shall confine our initial discussion to the carbon–carbon bond length in ethane. We may form hypothetical ethane molecules with differently hybridized carbon atoms by locating the hydrogen nuclei in such a manner as to force the appropriate changes in hybridization. The fact that such distorted molecules have insignificantly short lifetimes is of no consequence. We have performed a large number of INDO MO calculations on these ethane molecules in both the staggered and eclipsed conformation. In all cases the C–H bond lengths were assumed to be 1.09 Å. The C–C internuclear distances were varied and the equilibrium bond lengths, R_e, were obtained by minimizing the energy of the molecule with respect to this parameter.

For convenience, we imagine these molecules to be located at the origin of a Cartesian coordinate framework with the two carbon nuclei lying equidistant from the origin on the X axis. The geometry will be discussed in terms of the parameters R and θ shown in Figure 1.

A limitation of the localized σ bond description of saturated molecules can be visualized as follows. Consider ethane to be composed of a basis set of six hydrogen 1s orbitals and two sets of carbon 2s, $2p_x$, $2p_y$, and $2p_z$ orbitals centered on the appropriate nuclei. The two sets of three hydrogen 1s orbitals are most conveniently expressed as three normalized group orbitals, one (σ_1) symmetric with respect to the X axis and the other two (π_1, π_2) antisymmetric with respect to the XY XZ plane, respectively. Considering only those orbitals antisymmetric with respect to the XY plane, we obtain the picture shown in Figure 2.

These orbitals can be combined in the same manner as the four p_z orbitals in butadiene, with the same consequence: partial π bonding character between the two carbon atoms. A similar argument pertains to the orbitals antisymmetric with respect to the XZ plane.

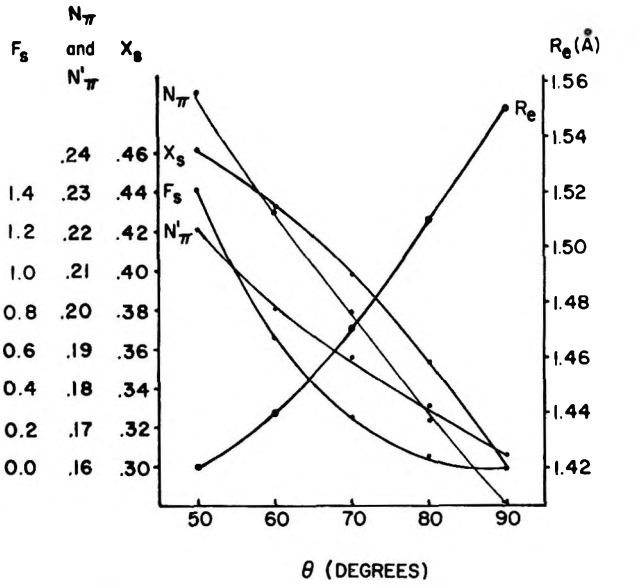

Figure 3.—The variation, as a function of the angle θ defined in the text, of (a) R_e, the calculated equilibrium bond length in Å, (b) N_π, the calculated pseudo π bond order between the two carbon atoms at the calculated equilibrium bond length, (c) N_π', the calculated pseudo π bond order between the two carbon atoms at a constant separation of 1.50 Å, and (d) F_s and X_s, two different estimates of fractional s character in the C–C bond, as defined in the text.

The formal hybridization of the carbon atoms is changed by the relocation of the hydrogen atoms. The effect of decreasing θ is to increase the s character in the C–C σ bond. If we assume complete absence of bond bending,[9] then the fractional s character (F_s) in the hybrid orbital on C_1 which is directed toward C_2 is given by[10]

$$F_s = 2 \cot^2 \theta$$

However, from Figure 2 it is apparent that the effect of decreasing θ is to decrease the π_1–p_z and π_1'–p_z' overlaps, and, since the mutual bond polarizability

$$\pi_{23,12} = \partial p_{23}/\partial \beta_{12}$$

is negative for butadiene,[12] this suggests that decreased π_1–p_z overlap resulting from a decrease in θ should result in an increase in the pseudo π bonding between the two carbon atoms. Consequently, any attempt to change the hybridization at carbon by changing bond angles will also be accompanied by a change in the pseudo π bond order. Furthermore, increased s character is accompanied by an *almost parallel* increase in pseudo π bond order, and both these factors should be borne in mind when interpreting experimental data.

The situation is best illustrated by some of the results of the INDO calculations. It is found that, as θ decreases, the calculated equilibrium bond length, R_e, decreases, as expected.[6] Figure 3 shows a plot of R_e *vs.* θ. It is noted that, for ethane ($\theta = 70°$),[13] R_e is somewhat smaller than the experimental value of 1.534 Å,[13] but the agreement is, nevertheless, quite satis-

(9) C. A. Coulson and W. E. Moffitt, *Phil. Mag.*, **40**, 1 (1949).

(10) Alternatively, to account for bond bending, θ could be replaced by θ_0, the angle between the x axis and the hybrid atomic orbital on carbon directed toward each hydrogen, and θ_0 could be estimated, for example, by the method of Mislow.[11]

(11) K. Mislow, *Tetrahedron Lett.*, 1415 (1964).

(12) A. Streitwieser, "Molecular Orbital Theory for Organic Chemists," Wile, New York, N. Y., 1961, pp 107, 108.

(13) H. C. Allen, Jr., and E. K. Plyler, *J. Chem. Phys.*, **31**, 1062 (1959).

factory. In order to examine the magnitude of the pseudo π bonding, the p_z–p_z' overlap populations[14] (n_π) were calculated at equilibrium bond length for each value of θ. These results are also shown in Figure 3. For the normal tetrahedral bond angle a substantial value of $n_\pi = 0.335$ is calculated, and in accord with the above reasoning this value increases as θ decreases.

In order to compare R_e with the s character calculated for the carbon–carbon bond, it is most convenient to consider the overlap populations of the carbon 2s orbital. If n (i, j) is the overlap population between orbitals i and j, then the extent (X_s) to which the 2s orbital on C_1 is involved in the total overlap population in the C_1–C_2 σ bond is given by [15]

$$X_s = \frac{n(C_1 2s,\ C_2 2s) + n(C_1 2s,\ C_2 2p_x)}{n(C_1 2s,\ C_2 2s) + n(C_1 2s,\ C_2 2p_x) + n(C_1 2p_x,\ C_2 2p_x)}$$

If this were a perfect criterion of hybridization, then a value of 0.25 would be expected for sp^3 hybrid orbitals and 0.33 for sp^2 orbitals, etc. Figure 3 shows F_s and X_s as a function of θ. It can be seen that there is a direct correlation between X_s and n_π thus making it extremely difficult to separate the two effects on a purely experimental basis. As a result, the conclusion of Maksić and Randić,[6] which neglected the pseudo π contributions, cannot be taken as an argument in support of bond shortening being the result of σ bond hybridizations. On the contrary, because of the close parallelism between X_s and n_π, the data are consistent with the conclusions of Miyazaki.[5]

It should be emphasized, however, that we do *not* claim to have established that the bond length variations are dependent *solely* upon the π or pseudo π bond order. On the contrary, because of the parallelism between this quantity and the fractional s character in the σ bond, it will be difficult to determine, on an experimental basis, which of these two quantities is responsible for the phenomenon.[18]

Registry No.—Ethane, 74-84-0.

(14) R. S. Mulliken, *J. Chem. Phys.*, **23**, 1841 (1955). Bond orders are strictly incompatible with the INDO approximations. The use of bond indice, however, leads to identical conclusions.

(15) The conclusions in this work are independent of the particular choice of definition of s character. For alternative definitions, see ref 16 and 17.

(16) C. Trindle and O. Sinanoglu, *J. Amer. Chem. Soc.*, **91**, 853 (1969).

(17) P. C. Van der Voorn and R. S. Drago, *ibid.*, **88**, 3255 (1966).

(18) NOTE ADDED IN PROOF.—W. R. Moore and C. R. Costin, *ibid.*, **93**, 4910 (1971), have recently presented dramatic evidence for the existence of pseudo π bonding in a bis(1-bicyclo[1.1.0]butyl) system. This molecule which lacks a formal chromophore shows an unusually long wavelength absorption (*ca.* 190 nm) and undergoes facile electrophilic addition to yield a 1,4-addition product in a manner analogous to that found in butadienes.

Notes

Quinoxaline Studies. XIX.[1] The Chiralities of the Bridge Carbon Atoms of (+)- and (−)-*trans*-Decahydroquinoxalines

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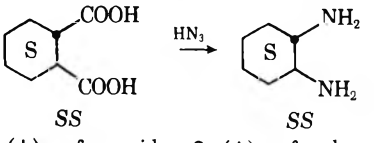
Received June 9, 1971

Discussion

The purpose of this publication, an epilogue of earlier work[2] and a prologue to future work, is to elucidate the chiralities of the bridge carbon atoms (C-9 and C-10) of the *trans*-decahydroquinoxalines, compounds which were earlier reported[2] and resolved. Applequist and Werner[3] and Mislow and coworkers,[4] reporting the chiralities of C-1 and C-2 of (+)-*trans*-cyclohexane-1(*S*),2(*S*)-dicarboxylic acid, bestowed feasibility upon this project.

(+)-*trans*-Cyclohexane-1(*S*),2(*S*)-dicarboxylic acid (**1**) was stereospecifically degraded *via* the Schmidt reaction to (+)-*trans*-cyclohexane-1(*S*),2(*S*)-diamine dihydrochloride (**2b**) in low yield (Scheme I). After the chiralities of C-1 and C-2 of **2b** had been established,

SCHEME I



SS *SS*

1, (+), as free acid **2a**, (+), as free base
b, (+), as dihydrochloride salt
c, (−), as (−)-tartrate salt

2c was more readily obtained by resolution of commerical 1,2-diaminocyclohexane with (−)-tartaric acid. Logistics dictated that the relatively large amounts of optically active *trans*-cyclohexane-1,2-diamine needed for preparation of the corresponding optically active *trans*-decahydroquinoxaline be obtained by resolution of 1,2-diaminocyclohexane with the cheaper (+)-tartaric acid. Scheme II displays the steps which related (−)-*trans*-cyclohexane-1(*R*),2(*R*)-diamine (**3a**) to (+)-*trans*-9(*R*),10(*R*)-decahydroquinoxaline (**5**).

With the chiralities of the bridge carbon atoms of **5** established, the chimera of a shorter, simpler route to this end then beckoned. This abbreviated route was based upon the reported reductive cycloalkylation[5] of

(1) Paper XVIII of this series: H. R. Moreno and H. P. Schultz, *J. Org. Chem.*, **36**, 1158 (1971).

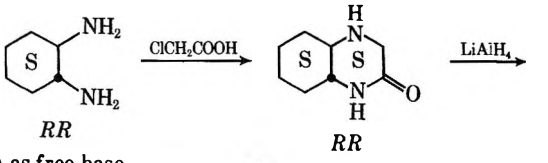
(2) E. Brill and H. P. Schultz, *ibid.*, **28**, 1135 (1963).

(3) D. E. Applequist and N. D. Werner, *ibid.*, **28**, 48 (1963).

(4) P. Laur, H. Häuser, J. E. Gurst, and K. Mislow, *ibid.*, **32**, 498 (1967).

(5) E. Brill and H. P. Schultz, *ibid.*, **29**, 579 (1964).

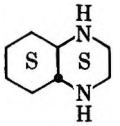
SCHEME II



RR

3a, (−), as free base
b, (−), as dihydrochloride salt
c, (+), as (+)-tartrate salt

4, (−), as free base



RR

5, (+), as free base

(±)-*trans*-cyclohexane-1,2-diamine with glyoxal to (±)-*trans*-decahydroquinoxaline.

To this earlier report is now added the observation that, with the conditions previously utilized,[5] **3a** was reductively cycloalkylated with glyoxal to optically active **5**. This success not only simplified the preparation of **5**, but also provided a measure of insight into the mode of formation of **5** *via* the reductive cycloalkylation of **3a**.

If the reductive cycloalkylation of **3a** to **5** had proceeded *via* either the intermediate addition compound (aminol) or dehydration compound (5,6,7,8,9,10-hexahydroquinoxaline), chiral integrities of the bridge carbon atoms of **5** would be expected to have been preserved. However, if formation of **5** in whole or part resulted from the intermediate, aromatic 5,6,7,8-tetrahydroquinoxaline (which could conceivably form by dehydrogenation of the hexahydroquinoxaline), then **5** would have been in part, at least, a racemic mixture. The result of this experiment indicates that the aromatic tetrahydroquinoxaline was not significantly present during the reductive cycloalkylation of **3a** to **5**.

Experimental Section[6]

(+)-*trans*-Cyclohexane-1(*S*),2(*S*)-dicarboxylic Acid (1).—(±)-*trans*-Cyclohexane-1,2-dicarboxylic acid[7] was resolved (68% yield) by the procedure of Applequist and Werner:[3] mp 183–185°, $[\alpha]^{26}D$ +22.25° (*c* 1.88, Me_2CO) [lit.[3] mp 183.5–185°, $[\alpha]^{30}D$ + 22.3° (*c* 5.3, Me_2CO)].

(+)-*trans*-Cyclohexane-1(*S*),2(*S*)-diamine Dihydrochloride (2b).—This material (**2b**) was prepared (13% yield) *via* the Schmidt reaction utilized by Yashunskii,[8] as modified by Brill and Schultz,[2] for the preparation of the corresponding cis isomer: $[\alpha]^{24}D$ +16.14° (*c* 0.21, H_2O) [lit.[9] $[\alpha]^{25}D$ ±15.8° (*c* 20)]. *Vide infra* for the optical activity of the enantiomeric hydrochloride.

(−)-*trans*-Cyclohexane-1(*S*),2(*S*)-diamine (−)-Tartrate (2c).—Commercial, redistilled 1,2-diaminocyclohexane[10] was resolved with (−)-tartaric acid (90% yield) by the procedure of Reinbold and Pearson[11] to give **2c**, $[\alpha]^{24}D$ −18.05° (*c* 0.44, H_2O). Its antipodal (+)-tartrate salt (**3c**) had $[\alpha]^{24}D$ +14.19° (*c* 0.32, H_2O) [lit.[11] $[\alpha]_{589}$ +12.1° (*c* 1, H_2O), lit.[12] $[\alpha]D$ +12°].

(+)-*trans*-Cyclohexane-1(*S*),2(*S*)-diamine (2a).—Solid potassium hydroxide was added to 50 ml of an aqueous, stirred solution containing 6.4 g of **2c** until two layers formed. The amine was separated and distilled from solid potassium hydroxide to give 2.25 g (81%) of colorless liquid **2a**, bp 104–110° (40 mm), $[\alpha]^{25}D$ +35.47° (*c* 4.74, Me_2CO). The optical antipode (**3a**) had bp 105–110° (40 mm), $[\alpha]^{25}D$ −35.20° (*c* 6.78, Me_2CO) [lit.[11] bp 75–80° (16 mm); lit.[13] bp 82° (14 mm), $[\alpha]D$ −36°]. The hydrochloride salt (**3b**) obtained upon passing hydrogen chloride gas into a diethyl ether solution of (−)-*trans*-cyclohexane-1(*R*),2(*R*)-diamine (**3a**) had $[\alpha]^{24}D$ −17.18° (*c* 0.51, H_2O) and $[\alpha]^{24}D$ −15.58° (*c* 20, H_2O) [lit.[9] $[\alpha]^{25}D$ ±15.8° (*c* 20)].

(−)-*trans*-9(*R*),10(*R*)-Decahydroquinoxalin-2-one (4).—Compounds **3b** and **3c** were cyclized with chloroacetic acid to **4** in 30% yields by the procedure of Brill and Schultz,[2] except that potassium bicarbonate was used instead of ammonium hydroxide: mp 196–197.5°, $[\alpha]^{24}D$ −70.33° (c 0.24, 95% EtOH).

Anal. Calcd for $C_8H_{14}N_2O$: C, 62.30; H, 9.15; N, 18.17. Found: C, 62.44; H, 9.12; N, 18.34.

The optical antipode of **4**, (+)-*trans*-9(*S*),10(*S*)-decahydroquinoxalin-2-one, was similarly prepared: mp 196–198°, $[\alpha]^{24}D$ +71.17° (*c* 0.45, 95% EtOH).

(+)-*trans*-9(*R*),10(*R*)-Decahydroquinoxaline (5). A. From 4.—Compound **4** was reduced to **5** with lithium aluminum hydride (50% yield) by the described procedure:[2] mp 176–177°, $[\alpha]^{24}D$ +16.31° (*c* 0.46, H_2O), $[\alpha]^{24}D$ +14.72° (*c* 0.4, 95% EtOH), and $[\alpha]^{24}D$ +10.72° (*c* 0.48, $CHCl_3$) [lit.[2] mp 176–177°, $[\alpha]^{26}D$ +10.4° (*c* 10, $CHCl_3$)]

Anal. Calcd for $C_8H_{16}N_2$: C, 68.52; H, 11.50; N, 19.98. Found: C, 68.79; H, 11.69; N, 20.35.

B. From 3a.—(−)-*trans*-Cyclohexane-1(*R*),2(*R*)-diamine was reductively cycloalkylated (30% yield) with glyoxal over platinum oxide catalyst by the earlier reported procedure.[5] The **5** obtained had mp 176–177°, $[\alpha]^{24}D$ +16.40° (*c* 0.38, H_2O).

Registry No.—**2a**, 21436-03-3; **2b**, 32044-18-1; **2c**, 32044-19-2; **3a**, 20439-47-8; **3b**, 32044-21-6; **3c**, 32044-22-7; (−)-**4**, 32044-23-8; (+)-**4**, 32044-24-9; **5**, 32044-25-0.

(6) Melting points, uncorrected, were determined on a Thomas–Hoover apparatus. All optical activities were determined in a Rudolph Model 63 polarimeter using a 2-dm tube. Microanalyses were performed by PCR, Gainesville, Fla.

(7) C. C. Price and M. Schwarcz, *J. Amer. Chem. Soc.*, **62**, 2891 (1940).

(8) V. G. Yashunskii, *Zh. Obshch. Khim.*, **28**, 1361 (1958); *Chem. Abstr.*, **52**, 19979*f* (1958).

(9) R. G. Asperger and C. F. Liu, *Inorg. Chem.*, **4**, 1492 (1965).

(10) Aldrich Chemical Co.

(11) P. E. Reinbold and K. H. Pearson, *Talanta*, **17**, 391 (1970). Their salt was named D(−)-*trans*-1,2-diaminocyclohexane L(+)-tartrate, although neither reference to nor proof of a known absolute configuration for the diaminocyclohexane moiety is presented. As written by Eliel (E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill, New York, N. Y., 1962, p 90), the use of only one configurational symbol is inadequate for naming a compound having two asymmetric atoms, even if the two centers are alike, as they are in (−)-*trans*-cyclohexane-1,2-diamine.

(12) R. S. Treptow, *Inorg. Chem.*, **5**, 1593 (1966). The salt was named *l*-chn *d*-tartrate, indicating that it was the salt of the (−)-free amine base with (+)-tartaric acid. In point of fact, the salt *itself*, as cited in the experimental details above, had a (+) rotation.

(13) F. M. Jaeger and L. Bijkerk, *Proc. Kon. Ned. Akad. Wetensch.*, **40**, 12 (1937); *Chem. Zentr.*, **108** (II) 1196 (1937).

Reactions of 2-Dichloromethylene-3-oxazolin-5-ones with Toluene under Friedel–Crafts Conditions

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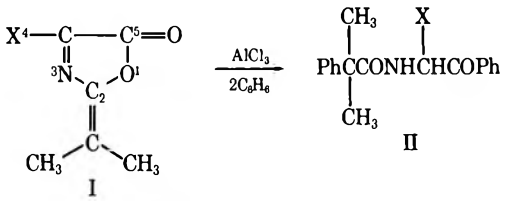
Received March 17, 1970

In our previous paper[1] it was reported that 2-isopropylidene-3-oxazolin-5-ones (I) react with benzene in the presence of anhydrous aluminum chloride to give 1:2 adducts, *N*-(α-phenylisobutyryl)-α-amino ketones (II), by 1,4 addition to the double bond system followed by ring opening.

It was of interest to determine what reaction would occur when related pseudoxazolones containing a di-

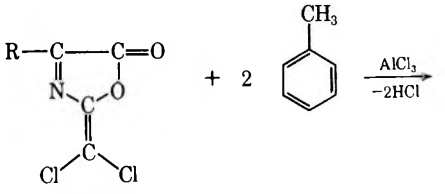
(1) Y. Iwakura, F. Toda, and Y. Torii, *J. Org. Chem.*, **32**, 3202 (1967).



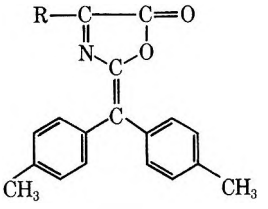
I II

X = Me, *i*-Pr, *i*-Bu, Ph

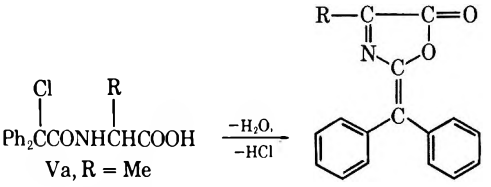
chloromethylene group, for example, 2-dichloromethylene-3-oxazolin-5-ones (III),[2] are treated under similar conditions. The major products isolated after the reaction of III with excess toluene in the presence of anhydrous aluminum chloride were shown to be 2-ditolylmethylene-3-oxazolin-5-ones (IV) by ir and nmr spectral comparison with the model compounds 2-diphenylmethylene-3-oxazolin-5-ones (VI), synthesized from *N*-diphenylchloroacetyl-DL-α-amino acids by a well-established route. Carbonyl absorption at 1770 cm^{-1} supports cyclic structures for the addition products.



IIIa, R = Me
b, R = *i*-Pr
c, R = *i*-Bu



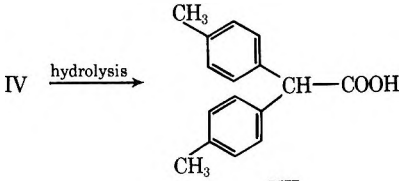
IVa, R = Me
b, R = *i*-Pr
c, R = *i*-Bu



Va, R = Me
b, R = *i*-Bu

VIa, R = Me
b, R = *i*-Bu

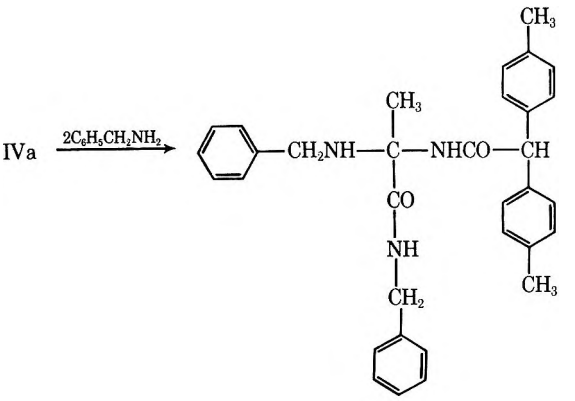
The nmr spectra are consistent with the assigned structures; the characteristic A_2B_2 pattern of the aromatic protons indicates para substitution of the tolyl groups. Substitution of two chlorine atoms of III could proceed by successive addition of toluene and elimination of labile hydrogen chloride as suggested by Steglich.[2] Di(*p*-tolyl)acetic acid (VII) was obtained from acid hydrolysis of IV.



VII

(2) W. Steglich, H. Tanner, and R. Hurnaus, *Chem. Ber.*, **100**, 1824 (1967).

It has been reported[3] that pseudoxazolones generally add 2 mol of primary amine. Compound IVa reacted spontaneously with 2 mol of benzylamine to give the 1:2 adduct VIII, presumably by 1,4 addition followed by ring opening.



VIII

Experimental Section

Reaction of 2-Dichloromethylene-3-oxazolin-5-ones with Toluene under Friedel–Crafts Conditions.—A sample of IIIa (2.22 g, 0.012 mol) in 100 ml of dry toluene was added dropwise to a stirred slurry of 7.14 g (0.054 mol) of anhydrous aluminum chloride in 50 ml of dry toluene. The reaction temperature was kept at 0° by the use of an ice bath. After the solution had been stirred for 2 hr, 40 ml of 18% HCl was added. The toluene layer was washed twice with 200-ml portions of water and dried (Na_2SO_4). After removal of toluene, the resulting solid was recrystallized from ethanol to give 1.91 g (53%) of IVa as a yellow solid: mp 141–142.5°; δ (CCl_4) 2.25 (s, 3) and 2.35 (s, 6). Similarly prepared were IVb [mp 128–132°; 84%; δ 1.3 (d, 6), 2.35 (s, 6), 3.00 (septet, 1)] and IVc [mp 118–119°; 54%; δ 0.95 (m, 6), 2.30 (s, 6), 2.40 (m, 3)].

Satisfactory analyses (0.35% for C, H, N) were reported for IVa and IVc. *Anal.* for IVb: C, 79.51. Calcd: C, 78.97.

Preparation of *N*-Diphenylchloroacetyl-DL-amino Acids (V).—To 7.3 g of DL-alanine, 21 g of *N*-chlorodiphenylacetyl chloride[4] in 200 ml of ethyl acetate was added. The mixture was refluxed for 14.5 hr. The reaction mixture was filtered, and the filtrate was washed with 200 ml of water and dried (Na_2SO_4). After removal of ethyl acetate, the resulting solid was recrystallized from benzene–cyclohexane to give *N*-diphenylchloroacetyl-DL-alanine, yield 9.7 g (38%), mp 134–135°.

Anal. Calcd for $C_{17}H_{16}ClNO_3$: C, 64.26; H, 5.07; N, 4.41; Cl, 11.16. Found: C, 64.48; H, 5.07; N, 4.17; Cl, 10.97.

Similarly prepared was *N*-diphenylchloroacetyl-L-leucine, yield 61%, mp 123–125°.

Anal. Calcd for $C_{20}H_{22}ClNO_3$: C, 66.75; H, 6.16; N, 3.89; Cl, 9.85. Found: C, 66.19; H, 6.05; N, 4.01; Cl, 9.79.

Synthesis of 2-Diphenylmethylene-3-oxazolin-5-ones (VI).—2-Diphenylmethylene-4-methyl-3-oxazolin-5-one (VIa) was prepared by the method used for the preparation of 2-dichloromethylene-3-oxazolin-5-ones (III) by Steglich, *et al.*[2]

N-Diphenylchloroacetyl-DL-alanine (6.8 g, 0.02 mol) was treated with 2 ml of phosphorus oxychloride and 7.4 ml of pyridine in 30 ml of methylene chloride to obtain 3.1 g (yield 59%) of 2-diphenylmethylene-4-methyl-3-oxazolin-5-one (VIa). The solid was recrystallized from ethanol: mp 155–156°; δ ($CDCl_3$) 7.65 (s, 3).

Anal. Calcd for $C_{17}H_{13}NO_2$: C, 77.55; H, 4.98; N, 5.32. Found: C, 77.47; H, 5.07; N, 5.28.

Similarly prepared was 2-diphenylmethylene-4-isobutyl-3-oxazolin-5-one (VIb). The solvent for recrystallization was ethanol: mp 70–72°; yield 58%; δ 0.98 (m, 6) and 2.46 (m, 3, $-CHCH_2-$).

Anal. Calcd for $C_{20}H_{19}NO_2$: C, 78.66; H, 6.27; N, 4.59. Found: C, 78.65; H, 6.24; N, 4.67.

(3) Y. Iwakura, F. Toda, Y. Torii, and K. Tomioka, *Tetrahedron*, **24**, 575 (1968).

(4) J. H. Billman and P. H. Hidy, *J. Amer. Chem. Soc.*, **65**, 760 (1943).

Hydrolysis of 2-Ditolylmethylene-3-oxazolin-5-ones (IV).—A sample (1.16 g) of IV was dissolved in 10 ml of dioxane. To this solution, 2.5 ml of concentrated HCl was added, and the mixture was kept at 80–90° for 9 hr. After evaporation of the reaction mixture, 100 ml of ether and 50 ml of 7% HCl were added. The layer of ether was collected. After evaporation of the ether the resulting solid was recrystallized from cyclohexane, yield 71% (0.68 g). This compound is *p,p*-ditolylacetic acid (VII), mp 137–138° (lit.[5] mp 144°).

Anal. Calcd for $C_{16}H_{16}O_2$: C, 79.97; H, 6.71. Found: C, 79.73; H, 6.73.

Hydrolysis of 2-ditolylmethylene-4-isopropyl-3-oxazolin-5-one gave the same compound.

Reaction of IVa with Benzylamine.—A mixture of IVa (1.49 g, 0.005 mol) and benzylamine (2.68 g, 0.025 mol) in benzene (10 ml) was kept at 80° for 5 hr. The resulting solid was collected by filtration and recrystallized from cyclohexane to give 2.1 g of crystals (VIII), yield 83%, mp 111.5–112.0°.

Anal. Calcd for $C_{33}H_{35}N_3O_2$: C, 78.33; H, 6.98; N, 8.31. Found: C, 78.30; H, 7.15; N, 8.43.

Registry No.—IVa, 30318-25-3; IVb, 30318-26-4; IVc, 30318-27-5; Va, 30318-28-6; Vb, 30318-29-7; VIa, 30318-30-0; VIb, 30318-31-1; VII, 20809-78-3; VIII, 30318-33-3; toluene, 108-88-3.

(5) P. Fritsch and F. Feldmann, *Justus Liebigs Ann. Chem.*, **306**, 72 (1899).

The Preparation and Some Reactions of 9-(Disubstituted amino)-9*H*-pyrrolo[1,2-*a*]indoles

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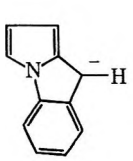
Received April 27, 1971

We wish to report a convenient method for the direct synthesis of 9-(*N*,*N*-disubstituted amino)-9*H*-pyrrolo-[1,2-*a*]indoles. At present, the only general procedure[2] for introducing substituents at the 9 position utilizes the anion I. Previous methods for preparing the 9*H*-pyrrolo[1,2-*a*]indole ring system II[3–5] also are not readily adaptable to permit 9-amino substitution.



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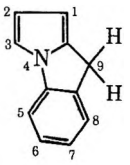
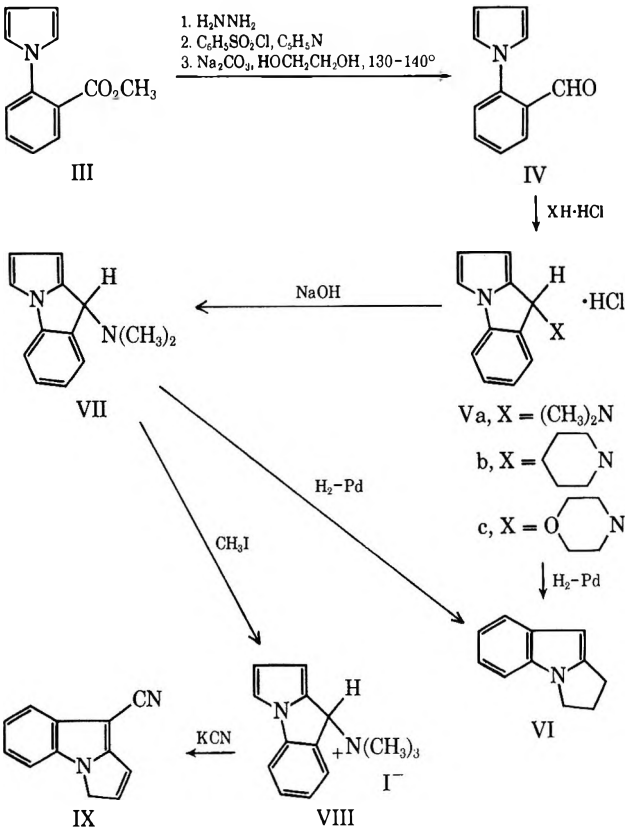


II

N-(*o*-Formylphenyl)pyrrole (IV) is prepared from *N*-(*o*-carbomethoxyphenyl) pyrrole (III) by a McFadden–Stevens reaction (Scheme I). Compound IV is converted directly to compounds Va–c by a Mannich reaction. The trimethylammonium iodide VIII also was prepared from Va. With two exceptions where acetaldehyde was successfully utilized as the carbonyl component,[6,7] Mannich reactions on pyrrole compounds have been limited to the use of formaldehyde.

SCHEME I



Catalytic reduction of the dimethylamino compound either as the free base VII or the hydrochloride salt Va is accompanied by prototropic tautomerism to give the known indole VI.[5] This is consistent with the work of Laschtuvka and Huisgen.[5]

Treatment of the quaternary ammonium compound VIII with potassium cyanide gave 9-cyano-3*H*-pyrrolo-[1,2-*a*]indole (IX). It was reported by Franck and Bernady[2] that treatment of the anion I with ethyl chloroformate or carbon dioxide also gives a 9-substituted 3-H derivative. As prototropic tautomerism took place in the former case where the pyrroloindole VIII is the electrophile as well as in the latter case where the pyrroloindole system (I) is the nucleophile and as the amino substituted compounds Va–e occur as 9-H derivatives, it appears that the 3-H compounds are the thermodynamically more stable products when the 9 position has an electron-withdrawing substituent and that 9-H compounds are favored when there is an electron-donating substituent at the 9 position.

Experimental Section

A Varian A-60A, Perkin-Elmer 137, and Cary recording spectrophotometer Model 14 were employed for obtaining spectral data. Uv. and ir spectra appear in Table I.

***o*-(Pyrrol-1-yl)benzohydrazide.**—Methyl *o*-(pyrrol-1-yl)benzoate[8] (III) (60.4 g, 0.3 mol), anhydrous hydrazine (200 ml), and ethanol (200 ml) were combined and stirred at reflux for 3 hr. The reaction mixture was next concentrated to a thick residue by rotary evaporation with the aid of heat. The residue crystallized to give a quantitative yield of product which was recrystallized

(1) Merrell National Laboratories, Division of Richardson-Merrell, Inc., Cincinnati, Ohio 45215.

(2) R. W. Franck and K. F. Bernady, *J. Org. Chem.*, **33**, 3050 (1968).

(3) E. E. Schweizer and K. K. Light, *ibid.*, **31**, 2913 (1966).

(4) G. R. Allen, Jr., and M. J. Weiss, *ibid.*, **30**, 2904 (1965). The 7-benzyloxy derivative was prepared in this paper.

(5) E. Laschtuvka and R. Huisgen, *Chem. Ber.*, **93**, 81 (1960).

(6) U. Eisner, *J. Chem. Soc.*, 854 (1957).

(7) W. Herz and U. Toggweiler, *J. Org. Chem.*, **29**, 213 (1964).

(8) A. D. Josey and E. L. Jenner, *ibid.*, **27**, 2466 (1962).

from chloroform: mp 123–125°; ir (Nujol) 3.10 (NH) and 6.11 μ (CO).

Anal. Calcd for $C_{11}H_{11}N_3O$: C, 65.67; H, 5.51; N, 20.88. Found: C, 65.66; H, 5.38; N, 20.73.

***N*-(*o*-Pyrrol-1-ylbenzoyl)-*N'*-benzenesulfonyl Hydrazine.**—To a stirred solution of *o*-(pyrrol-1-yl)benzohydrazide (4.0 g, 0.02 mol) dissolved in pyridine (25 ml) and cooled in an ice bath, benzenesulfonyl chloride (5.2 g, 0.03 mol) was added in a dropwise manner. After addition was complete, the stirring of the cooled reaction mixture was continued for 1 hr, and then the reaction mixture was poured onto an ice–hydrochloric acid mixture (100 g of ice and 100 ml of concentrated hydrochloric acid). A yellow solid formed which was removed by filtration and washed with dilute hydrochloric acid. After drying, the yellow product (4.3 g, 63%) was recrystallized from benzene: mp 151.5–153.5°; ir (Nujol) 3.10 (NH), 3.20 (NH), 6.08 (CO), 8.52 (SO_2), and 8.60 μ (SO_2).

Anal. Calcd for $C_{17}H_{15}N_3O_3S$: C, 59.81; H, 4.43; N, 12.31. Found: C, 59.96; H, 4.62; N, 12.63.

***o*-(Pyrrol-1-yl)benzaldehyde (IV).**—*N*-(*o*-Pyrrol-1-ylbenzoyl)-*N'*-benzenesulfonyl hydrazine (68.2 g, 0.2 mol) and ethylene glycol (800 ml) were stirred together while the temperature was slowly raised to 135°, at which time powdered anhydrous potassium carbonate (150 g) was added all at once. The reaction was stirred for 1.5 min and then cooled by the addition of warm water (500 ml). After cooling, the reaction mixture was extracted with ether which in turn was washed with water. The ether extracts were dried and filtered, and the solvent was removed, leaving a dark brown oil. Upon distillation of the oil, 16 g (47% yield) of product was collected at 70–72° (0.05 mm): ir (film) 3.60 (CH aldehyde), 3.70 (CH aldehyde), and 6.00 μ (CO).

Anal. Calcd for $C_{11}H_9NO$: C, 77.17; H, 5.30; N, 8.18. Found: C, 76.95; H, 5.10; N, 8.41.

General Procedure for the Preparation of 9-(*N*,*N*-Disubstituted amino)-9*H*-pyrrolo[1,2-*a*]indole Compounds (Va–c).—To a solution of disubstituted amine hydrochloride (0.05 mol) dissolved in a mixture of ethanol (30 ml) and methanol (20 ml) [for Va, only ethanol (50 ml) was used], compound IV (0.05 mol) was added rapidly and stirred for 3 hr at 25°. The products were precipitated by the addition of ether and separated by filtration: Va, nmr ($CDCl_3$) δ 2.72 (s, 6, CH_3), 5.57 (s, 1, HC-9), 6.44–6.70 (m, 2, HC-1, HC-2), 7.18–7.62 (m, 5, HC-3, HC-5–8), 8.52 (d, 1, HC-1).

9-*N*,*N*-Dimethylamino-9*H*-pyrrolo[1,2-*a*]indole (VII).—Va (1.0 g) was dissolved in water, made basic with a 10% aqueous sodium hydroxide solution, and extracted with ether. The dried ether extracts were concentrated, giving an oil which solidified on standing. The solid was sublimed at 62–68° (0.05 mm): nmr ($CDCl_3$) δ 2.17 (s, 6, CH_3), 4.85 (s, 1, HC-9), 6.12–6.43 (m, 2, HC-1, HC-2).

9-*N*,*N*-Dimethylamino-9*H*-pyrrolo[1,2-*a*]indole Methiodide (VIII).—To a solution of compound VII (3.9 g, 0.02 mol) dissolved in methanol (5 ml), methyl iodide (5 ml) was added. On standing in the cold, crystals were deposited which were separated by filtration: nmr ($CDCl_3$) δ 3.45 (s, 9, CH_3), 6.28–6.70 (m, 3, HC-1, HC-2, HC-9), 7.00–7.92 (m, 5, HC-3, HC-5–8).

9-Cyano-3*H*-pyrrolo[1,2-*a*]indole (IX).—To a stirred mixture of compound VIII (17.0 g, 0.05 mol) and water (100 ml), potassium cyanide (13.0 g, 0.2 mol) dissolved in water (100 ml) was rapidly added, followed by refluxing for 2 hr. A dark solid, filtered from the cooled reaction mixture, was extracted using hot ethanol which was next passed through a charcoal column. The ethanol (3.0 l.) was removed on a rotary evaporator and the residue was recrystallized: nmr ($CDCl_3$) δ 3.82 (s, 2, H_2C-3), 6.10–6.30 (m, 1, HC-2), 6.95 (d, 1, HC-1), 7.08–7.90 (m, 4, HC-5–8).

Reduction of 9-Dimethylamino-9*H*-pyrrolo[1,2-*a*]indole Hydrochloride (Va) and 9-Dimethylamino-9*H*-pyrrolo[1,2-*a*]indole (VII).—Compounds Va (0.01 mol) and VII (0.01 mol) were reduced in a Parr hydrogenator at 50 lb/in.^{2} over a 2-hr period utilizing ethanol (150 ml) as solvent and Pd–C (10%) as catalyst. The reduction of compound Va resulted in the uptake of 2 equiv of hydrogen while that of VII was slightly over 1 equiv. Prior to evaporation of the solvent in the case of compound Va, the catalyst was removed by filtration and dimethylamine hydrochloride (0.5 g) was precipitated by the addition of ether. With compound VII, after removal of catalyst, the solvent and dimethylamine, whose presence was shown by the strong amine odor, were removed on a rotary evaporator. The solid residues were recrystallized from ethanol. The reduction of hydrochloride salt Va gave a 65% yield while the free base, VII, gave 30% yield of product: mp 77–80° (lit.[5] 79–80°); uv max (ethanol) 281.9 mμ (lit.[5] 280 mμ).

Anal. Calcd for $C_{11}H_{11}N$: C, 84.04; H, 7.05; N, 8.91. Found: C, 84.21; H, 7.02; N, 8.77.

TABLE I

EXPERIMENTAL DATA[a]

No.	Yield, %	Mp, °C[b]	Recrystn solvent[c]	Uv spectra,[d] λ_{max}, mu (ε)	Ir spectra,[e] μ
Va	53	185	A–C	253 (12,000)	4.02 (NH^+)
				265 (10,000)	4.32 (NH^+)
Vb	44	210	A–C	252 (11,500)	3.92 (NH^+)
				266 (10,100)	4.13 (NH^+)
Vc	56	180	A–C	253 (11,300)	4.00 (NH^+)
				265 (10,000)	4.21 (NH^+)
VII		54–56		263 (10,900)	
VIII	98	130	B–C	255 (12,900)	
				270 (7,200)	
IX	50	106–108.5	A	260 (14,200)	4.58 (CN)
				271 (14,200)	
				275 (14,200)	
				282 (13,600)	
				292 (12,100)	
				95% EtOH	

[a] Satisfactory analytical data (±0.3% for C, H, N, and, when present, Cl) were reported for all compounds in table: Ed. [b] Decomposes. [c] A = ethanol, B = methanol, C = ether. [d] Va–c (methanol), VII–IX (95% ethanol). [e] Nujol.

Registry No.—IV, 31739-56-7; Va, 31739-57-8; Vb, 31739-58-9; Vc, 31739-59-0; VII, 31739-60-3; VIII, 31739-61-4; IX, 31739-62-5; *o*-(pyrrol-1-yl)-benzohydrazide, 31739-63-6; *N*-(*o*-pyrrol-1-ylbenzoyl)-*N'*-benzenesulfonyl hydrazine, 31739-64-7.

Pyrrole Studies. XVII.[1] Alkylation of Pyrrylthallium(I)

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Received May 24, 1971

Whereas alkylation of pyrrylmagnesium bromide with alkyl halides yields the isomeric 2- and 3-alkylpyrroles as the major products, alkylation of alkali metal salts of pyrrole gives, with few exceptions, the 1-substituted compounds as the predominant products with only small amounts of the C-alkylated compounds. The position of electrophilic attack on the pyrryl anion appears, however, to be determined largely by the ionic radius of the alkali metal ion and the polarity of the solvent and significant variations in the isomer ratios have also been observed with different alkyl halides.[2]

The similarity in the ionic radius of K^+ and Tl^+ (1.33 and 1.47 Å, respectively) prompted a study of pyrrylthallium(I) and its reaction with alkyl halides. More-

(1) Part XVI: C. F. Candy and R. A. Jones, *J. Chem. Soc. C*, 1405 (1971).

(2) For a summary of references, see K. Schofield, "Heteroaromatic Nitrogen Compounds: Pyrroles and Pyridines," Butterworth, London, 1967; R. A. Jones, *Advan. Heterocycl. Chem.*, **11**, 383 (1970).

over, previous studies[3,4] have already shown that acylation of pyrrylthallium(I) with acyl chlorides occurs very readily to give the 1-acylpyrroles in considerably better yields than from the procedure using pyrrylpotassium.

Pyrrylthallium(I) was readily isolated from the reaction of thallium ethoxide with pyrrole[3,4] and, compared with pyrrylpotassium, it is a relatively stable solid, only slightly light sensitive and almost completely inert to atmospheric water. It is insoluble in organic solvents and is not decomposed in cold water. Dilute aqueous acids, however, regenerate pyrrole. The precise structure of pyrrylthalluim(I) is unknown, but the similarity of its ^{1}H nmr spectrum measured in diethyl ether (triplets at τ 3.15 and 3.74, J = 2 Hz) with those of pyrrylsodium[5] and pyrrylmagnesium bromide[5,6] suggests an ionic or ion-pair structure.

With the exception of the reactions with ethyl iodide and *tert*-butyl iodide, pyrrylthallium(I) reacted with alkyl iodides to give the corresponding 1-alkylpyrroles in high yield to the exclusion of C-alkylated products (Table I). No attempts were made to optimize the yields by varying the reactions conditions, but the experimental simplicity of the method, compared with that using pyrrylpotassium, recommends it as a superior method for the N-alkylation of pyrroles. The low yields of 1-ethyl- and 1-*tert*-butylpyrrole, with the concomitant formation of pyrrole, are most probably due to the preferential β elimination of hydrogen iodide, induced by the pyrryl anion, from the alkyl iodides.

1-Methyl- and 1-ethylpyrrole were also isolated in 57 and 62% yield, respectively, from the reaction of the corresponding alkyl tosylate and pyrrylthallium(I) at 60° over 20 hr, but alkyl chlorides and bromides were found to react less readily. Preliminary investigations also suggest that thallium salts may be used with equal success in the N-alkylation of substituted pyrroles; *e.g.*, the thallium(I) salt of 2-formylpyrrole with methyl iodide gave an almost quantitative yield of 1-methyl-2-formylpyrrole.

TABLE I

ALKYLATION OF PYRRYLTHALLIUM(I)

Alkylating agent	Reaction time, hr	Reaction temp, °C	Yield of purified 1-alkylpyrrole,[a] %
Methyl iodide	14	20	98 (99)
Ethyl iodide	24	60	51[b]
Propyl iodide	24	60	68 (98)
Isopropyl iodide	24	60	95 (98)
n-Butyl iodide	32	60	82 (97)
tert-Butyl iodide	15	60	15[c]
Trimethylsilyl chloride	1	20	93 (97)
Benzyl bromide	20	20	82 (96)

[a] Yields, based on pyrrylthallium(I) consumed, of products isolated by distillation. Figures given in parentheses give the purity of the product before distillation. All products were identified by nmr spectroscopy (Table II). [b] Pyrrole (38%) and unidentified product (11%) detected. [1,2-Diethylpyrrole was not detected. *Cf.* reaction of ethyl iodide with pyrrylpotassium: G. Ciamician and C. M. Zannetti, *Ber.*, **22**, 659 (1889).] [c] Pyrrole (84%) recovered.

TABLE II

^{1}H NMR DATA FOR 1-SUBSTITUTED PYRROLES[a]

1 substituent	Registry no.	Pyrrole ring protons[b] α	Pyrrole ring protons[b] β	Substituent protons[b]
Me[c,d]	96-54-8	3.67	3.97	6.84 (CH_3)
Et[c,d]	617-92-5	3.51	3.90	6.40 (CH_2), 8.87 (CH_3)
n-Pr	5145-64-2	3.47	3.91	6.42 (NCH_2), 8.42 (CH_2), 9.16 (CH_3)
i-Pr[d]	7057-97-8	3.45	3.90	6.19 (CH), 8.85 ($C(CH_3)_2$)
n-Bu	589-33-3	3.45	3.99	6.25 (NCH_2), 7.85–8.60 (CH_2CH_2), 9.15, (CH_3)
tert-Bu[d]	24764-40-7	3.35	4.00	8.64 ($C(CH_3)_3$)
$Si(CH_3)_3$	18276-53-4	3.37	3.84	9.79 ($Si(CH_3)_3$)
CH_2Ph[c,d]	2051-97-0	3.52	3.77	2.85–3.25 (C_6H_5), 5.46 (CH_2)

[a] Solvent $CDCl_3$. [b] Chemical shifts (τ) in parts per million (ppm). [c] *Cf.* R. A. Jones, T. McL. Spotswood, and P. Cheuychit, *Tetrahedron*, **23**, 4469 (1967). [d] Data identical with that for the compound prepared from 2,5-diethoxytetrahydrofuran and the appropriate amine.[4]

Experimental Section

Alkylation of Pyrrylthallium(I).—Pyrrylthallium(I) (0.04 mol) was stirred with the appropriate alkyl halide (0.1 mol) in the absence of a solvent in a flask from which the light was excluded and under the conditions given in Table I. The thallium(I) halide was filtered off and washed with dry ether, and the combined filtrates were analyzed by glpc on a Perkin-Elmer 452 gas chromatograph using a 1 m × 0.25 in. (o.d.) polypropylene glycol on Celite (20:80 w/w) column at 100° with a nitrogen inlet pressure of 15 psig.

1-Methyl-2-formylpyrrole.—The thallium(I) salt of 2-formylpyrrole (0.003 mol), prepared from 2-formylpyrrole and thallium(I) ethoxide, was stirred in the absence of a solvent with methyl iodide (0.01 mol) at room temperature for 5 hr. After removal of the thallium(I) iodide, distillation of the filtrate gave 1-methyl-2-formylpyrrole (91%) which was identical in all respects with a sample prepared by the formylation of 1-methylpyrrole.[4]

Registry No.—Pyrrylthallium(I), 31981-10-9.

(3) M. J. Zalesko, Ph.D. Thesis, Princeton University, 1970.

(4) C. F. Candy, R. A. Jones, and P. H. Wright, *J. Chem. Soc. C*, 2563 (1970).

(5) M. G. Reinecke, H. W. Johnson, and F. F. Sebastian, *J. Amer. Chem. Soc.*, **85**, 2859 (1963).

(6) A. J. Castro, J. F. Deck, N. C. Ling, J. P. Marsh, and G. E. Means, *J. Org. Chem.*, **30**, 344 (1965).

Reaction of Azobenzene with Triphenylphosphine

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Received June 22, 1971

Diethyl azodicarboxylate reacts vigorously with triethyl phosphite in ether solution to form a 1:1 adduct, described as a colorless, mobile oil.[1] Triphenylphosphine was also reported to react with the azo ester to form a yellowish-white precipitate which became resinous. This material was not characterized but did yield triphenylphosphine oxide on shaking with water.[1]

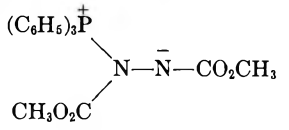
A number of esters of azodicarboxylic acid, phenyl diazosulfone, and 2,2′,4,4′,6,6′-hexanitroazobenzene were reported to react readily with triethyl and triphenyl phosphite to form adducts.[2] However, the phosphite was believed to add to the carbonyl group of

(1) D. C. Morrison, *J. Org. Chem.*, **23**, 1072 (1958).

(2) V. A. Ginsburg, M. N. Vasil'eva, S. S. Dubov, and A. Ya. Yakubovich, *Zh. Obshch. Khim.*, **30**, 2854 (1960); *Chem. Abstr.*, **55**, 17477 (1961).

the esters rather than the azo linkage. Azobenzene was reported to be unreactive toward the phosphite esters. Triphenylphosphine reacted with diethyl azodicarboxylate in ether with Dry Ice cooling to give a red solid which formed a "sticky mass" at room temperature and was not characterized.[2]

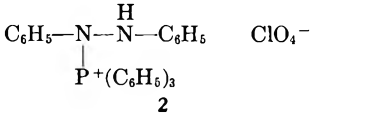
The adduct which formed between triphenylphosphine and dimethyl azodicarboxylate was produced in solution and found to undergo a variety of cycloaddition reactions with a number of reagents.[3] Apparently the adduct was not isolated. A quasi-1,3-dipole structure was suggested for the adduct as shown in **1**. The tri-



1

phenylphosphine–diethyl azodicarboxylate adduct was found to catalyze the reaction between the azo ester and several mercaptans to yield disulfides and diethyl hydrazodicarboxylate.[4] The phosphine was recovered unchanged. Formation of the phosphine–azo ester adduct was observed by the decrease in absorption of the azo group at 405 nm.

We have found that azobenzene reacts readily with triphenylphosphine at room temperature in aqueous ethanol or methanol containing perchloric acid to form a 1:1:1 adduct of the azo compound, phosphine, and perchloric acid. The reaction can be followed in dilute solution by observing the decrease in absorption of the azo group at 320 nm or the decrease in the polarographic reduction wave for the azo linkage, $E_{1/2} = -0.05$ V *vs.* sce, in perchloric acid solution. In higher concentrations the adduct precipitates in high yield (80–85%) after 5–10 min. The adduct is believed to have the following structure **2**. It appears to be stable, melts



2

to a red-brown liquid at 169–171°, and is very soluble in acetonitrile, dimethylformamide, and dimethyl sulfoxide and does not appear to dissolve in ethanol or water. The infrared spectrum of the compound has numerous peaks characteristic of the phenyl group and an absorption peak at 3200 cm^{-1} which is believed to be due to the N–H stretching mode. The nmr spectrum shows one signal with several peaks at δ 6.7–7.5, a second multipeak signal at δ 7.5–8.4, and a single peak at δ 9.4. These signals have relative areas, in the order given, of 10:14.6:1.3. The nmr spectrum is in agreement with the suggested structure. The uv spectrum has a maximum at 270 nm (ϵ 8000) and end absorption increasing from 240 nm.

The adduct was successfully titrated with KOH in acetonitrile, dimethylformamide, dimethyl sulfoxide, and pyridine. Glass and calomel electrodes were used and a reasonably large (250 mV) break in the potentiometric curve was found. The solutions turned yellow on reacting with base, presumably indicating the regeneration of azobenzene. The equivalent weight was found to be 530, as compared to the calculated value of 545. Other aromatic azo compounds, 4,4′-azodianiline and 4,4′-azodiphenetole, were found to react slowly with triphenylphosphine under the same conditions, but no products were isolated. No reaction was observed between azobenzene and tributylphosphine.

This reaction would appear to be similar to those involving the addition of tertiary phosphines to activated carbon–carbon double bonds.[5] Triphenylphosphine adds to the carbon–carbon double bond of benzalmalononitrile to form an adduct which then adds HCl to give a phosphonium chloride.[6]

(3) E. Brunn and R. Huisgen, *Angew. Chem., Int. Ed. Engl.*, **8**, 513 (1969).

(4) K. Kato and O. Mitsunobu, *J. Org. Chem.*, **35**, 4227 (1970).

Experimental Section

Materials.—Azobenzene and triphenylphosphine were Eastman Reagent chemicals. All other chemicals and solvents were the best available reagent grade materials.

Methods.—Infrared spectra were recorded with a Beckman IR-20 spectrophotometer. A Beckman DK-2A instrument was used to measure uv absorption. The nmr spectra were obtained with a Varian A-60A spectrometer.

Potentiometric titrations were done with a Corning Model 111 digital pH meter equipped with glass and calomel electrodes. A Hewlett–Packard Model 185 CHN analyzer was used for the C, H, and N analyses. The phosphorus analysis was by the Galbraith Laboratories, Knoxville, Tenn.

Preparation of the Adduct.—A solution of azobenzene (1.82 g, 10 mmol) and triphenylphosphine (2.62 g, 10 mmol) was prepared in 100 ml of 95% ethanol; 2 ml of 72% $HClO_4$ (23 mmol) was added to this solution. Precipitation of the adduct began within 5 min. The crystals were filtered after 1 hr and washed with ethanol. A yield of 4.63 g (85%) was obtained. The compound melts with decomposition to a red-brown liquid at 169–171°. The adduct was also prepared using aqueous methanol (10% H_2O) as solvent with about the same yield.

Anal. Calcd for $C_{30}H_{26}ClN_2O_4P$: C, 66.1; H, 4.82; N, 5.13; P, 5.69. Found: C, 65.8; H, 4.68; N, 5.28; P, 5.63.

Potentiometric Titrations.—Weighed amounts (0.05–0.2 mmol) of the adduct were titrated with standard solutions of KOH (0.02–0.04 *M*) in ethanol. Reaction was rapid and reasonably stable readings were obtained in dimethyl sulfoxide. The equivalent weight found was 530, compared with a calculated value of 545.

Registry No.—**2**, 32120-81-3; azobenzene, 103-33-3; triphenylphosphine, 603-35-0.

Acknowledgment.—The authors thank Dr. James E. Johnson of Texas Woman's University for recording the nmr spectra. The support of the Robert A. Welch Foundation of Houston, Texas, is gratefully acknowledged.

(5) S. Patai and Z. Rappoport in "The Chemistry of Alkenes," S. Patai, Ed., Interscience, New York, N. Y., 1964, pp 506–508.

(6) J. A. Ford, Jr., and C. V. Wilson, *J. Org. Chem.*, **26**, 1433 (1961).

A Novel Two-Step Synthesis of 10*H*-Benz[*b*]indeno[2,1-*d*]thiophene. Heterocyclopentadienes. III

THOMAS J. BARTON,* A. JAMES NELSON,[1] AND JON CLARDY

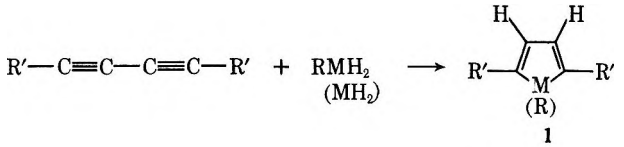
Department of Chemistry, Iowa State University, Ames, Iowa 50010

Received May 11, 1971

A particularly successful method for the synthesis of monoheterocyclopentadienes (**1**) is the addition of

(1) NASA Predoctoral Fellow, 1969–present.

RMH_2 (M = P,[2] As,[3] N[4]) and MH_2 (M = S,[5] Se,[6] Te[7]) to 1,3-diynes. An attractive extrapolation of this route to the synthesis of heterocycloheptatrienes would involve the addition of RMH_2 or MH_2 to 1,5-diyn-3-enes. We have investigated this route with H_2S and the readily available *o*-bis(phenylethynyl)benzene[8] (**2**) in hopes of preparing 2,4-diphenylbenzo[*b*]thiepin (**3**) in a convenient one-step synthesis. This reaction was originally planned as a model route for the unknown selenepin and tellurepin ring systems. However, when hydrogen sulfide was passed through a refluxing solution of **2** in aqueous acetone (135 ml of water and 15 ml of 1 *N* sodium hydroxide for 2.78 g of **2**) the sole isolable product was **2**. Likewise refluxing **2** in methanolic potassium sulfide afforded **2** as the only characterizable material. Further attempts to bring about the desired conversion of **2** → **3** by addition of hydrogen sulfide were not made.



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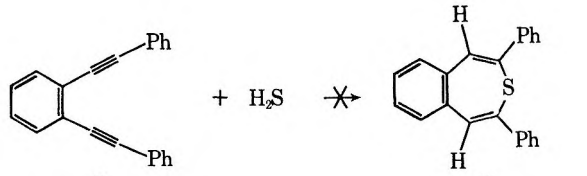
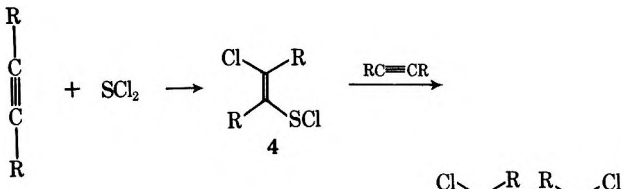


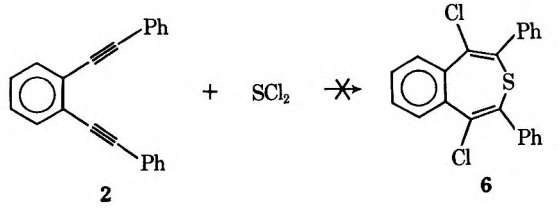
2 **3**

Another possible one-step route to a benzo[*d*]thiepin from **2** can be envisioned from the addition of sulfur dichloride. The addition of sulfur dichloride to acetylenes is known to proceed through an often isolable vinyl sulfenyl chloride (**4**)[9] which can add to another molecule of acetylene to afford a β,β'-dichlorodivinyl sulfide (**5**).[10] It has also been shown that SCl_2 will add to 1,3-diynes to yield 3,4-dichlorothiophenes.[11] It was therefore hoped that the conversion of **2** → **6** could be easily effected.

Since SCl_2 is an electrophilic reagent, whose reactions with acetylenes are thought to proceed through a thirene type intermediate which suffers nucleophilic attack by chloride anion,[9] one must consider the known behavior of **2** with electrophiles before predicting the course of this reaction. Whitlock[8] has reported that



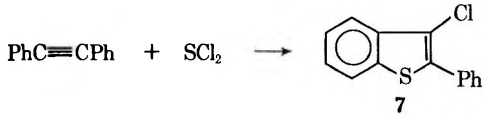
4 **5**



2 **6**

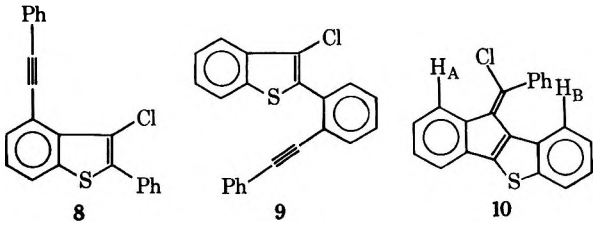
electrophilic attack on **2** results in formation of diphenylbenzofulvenes, or ring systems derived therefrom, without exception. This, of course, results from interaction of the triple bonds in the addition step. However, since it is questionable how much of the positive charge in the intermediate derived from SCl_2 addition to an acetylene resides on carbon, we could not confidently predict a similar course for SCl_2.

Several routes by which SCl_2 might react with **2** may be mechanistically envisioned and a choice between them is difficult. We therefore assumed that a mixture of products would likely result and hoped that **6** would represent a significant fraction of this mixture. Neither of these things turned out to be the case. Addition of SCl_2 to **2** provides a 90% yield of *one* product which analyzes for **6** less the elements of hydrogen chloride. The most striking feature of this orange, crystalline material is its nmr spectrum, which consists solely of two gross multiplets in the aromatic region (δ 8.5–8.3, 7.5–6.3; 12 H) and two peaks in the olefinic region (δ 5.6, 5.45; 1 H) which are actually multiplets upon high resolution. The loss of HCl is easily rationalized when one considers the known reaction of SCl_2 and diphenylacetylene to give 3-chloro-2-phenylbenzo[*b*]thiophene (**7**).[9]



7

Reasonable structures which can be drawn for the molecular formula, $C_{22}H_{13}SCl$, solely on mechanistic considerations are **8**, **9**, and **10**. However, examination of models of these three molecules makes a choice of **10** very easy on the basis of the nmr spectrum. Regardless of the stereochemistry of the exocyclic chlorobenzylidene unit, either H_A or H_B is pushed into the

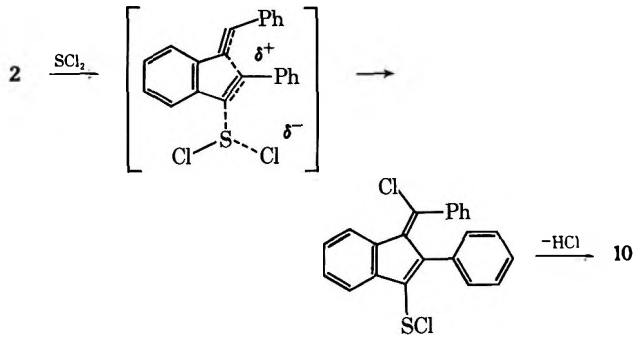


8 **9** **10**

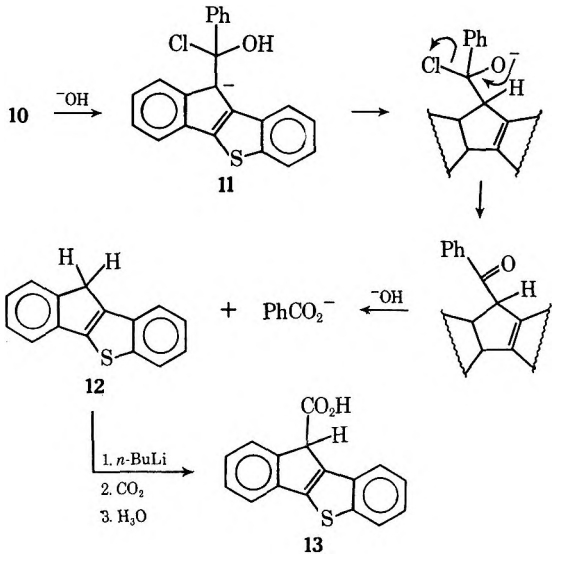
(2) E. A. Braye, IUPAC Symposium on Organo-Phosphorus Compounds, Heidelberg, 1964; G. Märkl and P. Potthast, *Angew. Chem.*, **79**, 58 (1967).
(3) G. Märkl and H. Hauptmann, *Tetrahedron Lett.*, 3257 (1968).
(4) J. Reisch and K. E. Schulte, *Angew. Chem.*, **73**, 241 (1961); K. E. Schulte, J. Reisch, and H. Walker, *Arch. Pharm. (Weinheim)*, **299**, 1 (1966).
(5) K. E. Schulte, J. Reisch, and L. Hörner, *Angew. Chem.*, **72**, 920 (1960); *Chem. Ber.*, **95**, 1943 (1962); K. E. Schulte, J. Reisch, W. Hermann, and G. Bohn, *Arch. Pharm., (Weinheim)*, **296**, 456 (1963); K. E. Schulte, J. Reisch, and W. Hermann, *Naturwissenshaften*, **50**, 332 (1963); K. E. Schulte and G. Bohn, *Arch. Pharm. (Weinheim)*, **297**, 179 (1964); K. E. Schulte, G. Rücker, and W. Meinders, *Tetrahedron Lett.*, 659 (1965).
(6) R. F. Curtis, S. N. Hasnain, and J. A. Taylor, *Chem. Commun.*, 365 (1968).
(7) W. Mack, *Angew. Chem., Int. Ed. Engl.*, **5**, 896 (1966).
(8) H. W. Whitlock, Jr., and P. E. Sandvick, *J. Amer. Chem. Soc.*, **88**, 4525 (1966).
(9) T. J. Barton and R. G. Zika, *J. Org. Chem.*, **35**, 1729 (1970).
(10) L. Brandsma and J. F. Arens, *Recl. Trav. Chim. Pays-Bas*, **80**, 237 (1961).
(11) K. E. Schulte, H. Walker, and L. Rolf, *Tetrahedron Lett.*, 4819 (1967). Reference 10 represents the first report of the addition of SCl_2 to an alkyne (divinyl sulfide preparations) while ref 11 reports the first additions of SCl_2 to 1,3-diynes (dichlorothiophene preparations). We were unaware of these two reports and thank Professor Schulte for informing us of his work.

shielding cone of the phenyl ring, thus explaining the prominent upfield shift of a single proton. Rotation of this phenyl ring is prevented by H_A or H_B.

A rational mechanism for the formation of **10** involves electrophilic attack of SCl_2 on one acetylenic linkage of **2** with concomitant involvement of the other triple bond as postulated by Whitlock[8] for the addition of bromine and hydrogen bromide. The intermediate sulfenyl chloride could then attack a phenyl ring to afford **10**.



As **10** represents to our knowledge the first example of the benz[*b*]indeno[2,1-*d*]thiophene ring system,[12] we were quite interested in converting it into the parent system. This was easily accomplished by treatment of **10** with potassium hydroxide in hot triethylene glycol. This procedure affords 10*H*-benz[*b*]indeno[2,1-*d*]thiophene (**12**) in *ca.* 50% yield. The conversion may be viewed as proceeding through initial attack by hydroxide ion on the exocyclic double bond so as to yield the indenyl anion (**11**) followed by several straightforward steps ending with a reverse condensation. The title compound (**12**) can be easily converted into the 10-acid (**13**) through treatment with *n*-butyllithium and then CO_2.



Final, conclusive proof of **12** was obtained by X-ray crystallography. The molecular structure of **12** is shown in Figure 1.

(12) See D. W. H. MacDowell and A. T. Jeffries, *J. Org. Chem.*, **35**, 871 (1970); D. W. H. MacDowell and T. B. Patrick, *ibid.*, **32**, 2441 (1967), for the synthesis and chemistry of indenothiophenes.

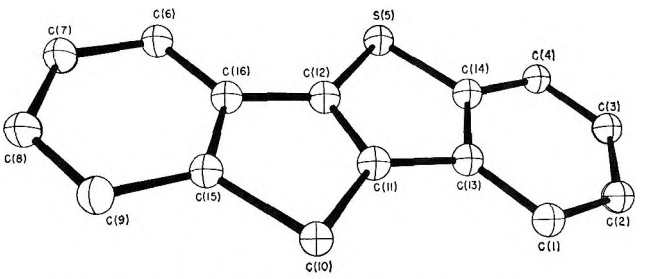


Figure 1.—The molecular structure of adduct **12**.

Experimental Section

Infrared spectra were recorded on a Perkin-Elmer Model 21 spectrophotometer. Proton nmr spectra were determined on a Perkin-Elmer R-20-B instrument. Analyses were carried out by Ilse Beetz Mikroanalytisches Laboratorium, Kronach, West Germany.

Commercial sulfur dichloride (Matheson Coleman and Bell) was purified as in ref 9. *o*-Bis(phenylethynyl)benzene (**2**) was prepared by the method of Whitlock[13] and purified by chromatography on Woelm neutral alumina (hexane elution) followed by recrystallization from hexane [mp 49.1–50.5° (lit.[13] mp 49.5–51.5°)].

Addition of Sulfur Dichloride to *o*-Bis(phenylethynyl)benzene. 10-(Chlorobenzylidene)benz[*b*]indeno[2,1-*d*]thiophene (10).—Solutions of 1.19 g (4.27 mmol) of *o*-bis(phenylethynyl)benzene and 0.516 g (5.03 mmol) of freshly distilled sulfur dichloride each in 100 ml of dry methylene chloride were simultaneously added to 1.2 l. of stirred, refluxing methylene chloride. The addition was complete after 45 min and the resultant brilliant red solution was refluxed an additional 15 min. The solvent was removed *in vacuo* to leave a crude red solid. Recrystallization from methylene chloride–hexane afforded 1.323 g (90.3%, mp 169–171°) of orange, crystalline **10**: mp 175°; ir (KBr) 6.25, 6.95, 7.40, 8.15, 9.35, 9.75, 10.75, 11.05, 13.15, 13.35–13.55, 14.50 μ; nmr ($DCCl_3$) δ 8.5–8.3 and 7.5–6.3 (m, 12 H), 5.6 and 5.45 (m, 1 H); mass spectrum *m/e* 344 (100%, M^+), 346 (40.7%, M + 2^+).

Anal. Calcd for $C_{22}H_{13}SCl$: C, 76.62; H, 3.80; Cl, 10.28. Found: C, 76.58; H, 3.85; Cl, 10.31.

Oxidation of 10 with *m*-Chloroperbenzoic Acid. 10-(Chlorobenzylidene)benz[*b*]indenyl[2,1-*d*]thiophene 1,1-Dioxide.—To a solution of 0.501 g (1.46 mmol) of **10** in 30 ml of ice-bath cooled chloroform was added 0.453 g (2.63 mmol) of *m*-chloroperbenzoic acid in *ca.* 40 ml of chloroform. The reaction mixture was kept at ice-bath temperature for an additional 5 min and then allowed to stand at room temperature for 24 hr. After filtration the reaction solution was percolated through a 2.7 × 40 cm column of silica gel packed in hexane. The fraction eluted with hexane was stripped of solvent, dissolved in methylene chloride, washed with dilute potassium carbonate solution, dried over magnesium sulfate, and filtered, and the solvent was evaporated to a minimum volume. Addition of *n*-hexane and cooling afforded 0.302 g (55%) of the bright red crystalline sulfone of **10**: mp 210–211°; ir (KBr) 6.40, 6.95, 7.75, 8.70, 10.60 μ; nmr ($DCCl_3$) δ 8.6–8.4 and 7.8–6.8 (m, 12 H), 5.25 and 5.10 (m, 1 H); mass spectrum *m/e* 376 (100%, M^+), 378 (41.7%, M + 2^+).

Anal. Calcd for $C_{22}H_{13}O_2SCl$: C, 70.2; H, 3.48; O, 8.5; Cl, 9.42. Found: C, 69.82; H, 3.88; O, 8.58; Cl, 9.55.

10H-Benz[*b*]indeno[2,1-*d*]thiophene (12).—To a solution of 1.3 g of potassium hydroxide in 50 ml of triethylene glycol at *ca.* 150° was added 0.789 g (2.29 mmol) of **10**. The solution was heated intermittently with a Bunsen burner for *ca.* 5 min while stirring. After cooling, 100 ml of water was added and the solution was extracted with methylene chloride (two 100-ml portions). The organic layers were combined, washed with water, dried over magnesium sulfate, and filtered and the solvent was removed *in vacuo*. The residue was dissolved in a small amount of methylene chloride and percolated through a 6 × 6 cm column of silica gel packed with hexane. Concentration of the fraction eluted with hexane resulted in precipitation of 0.268

(13) H. W. Whitlock, Jr., P. E. Sandvick, L. E. Overman, and P. B. Reichardt, *J. Org. Chem.*, **34**, 879 (1969).

g (53%) of red **12**. Sublimation yielded a light yellow analytical sample: mp 201–202°; ir 6.25, 6.90, 8.0, 9.90, 10.10, 13.45, 13.75, 14.00 μ; nmr ($DCCl_3$) δ 7.9–7.2 (m, 8 H), 3.8 (s, 2 H); mass spectrum m/e 222 (100%, M^+), 224 (7.5%, $M + 2^+$).

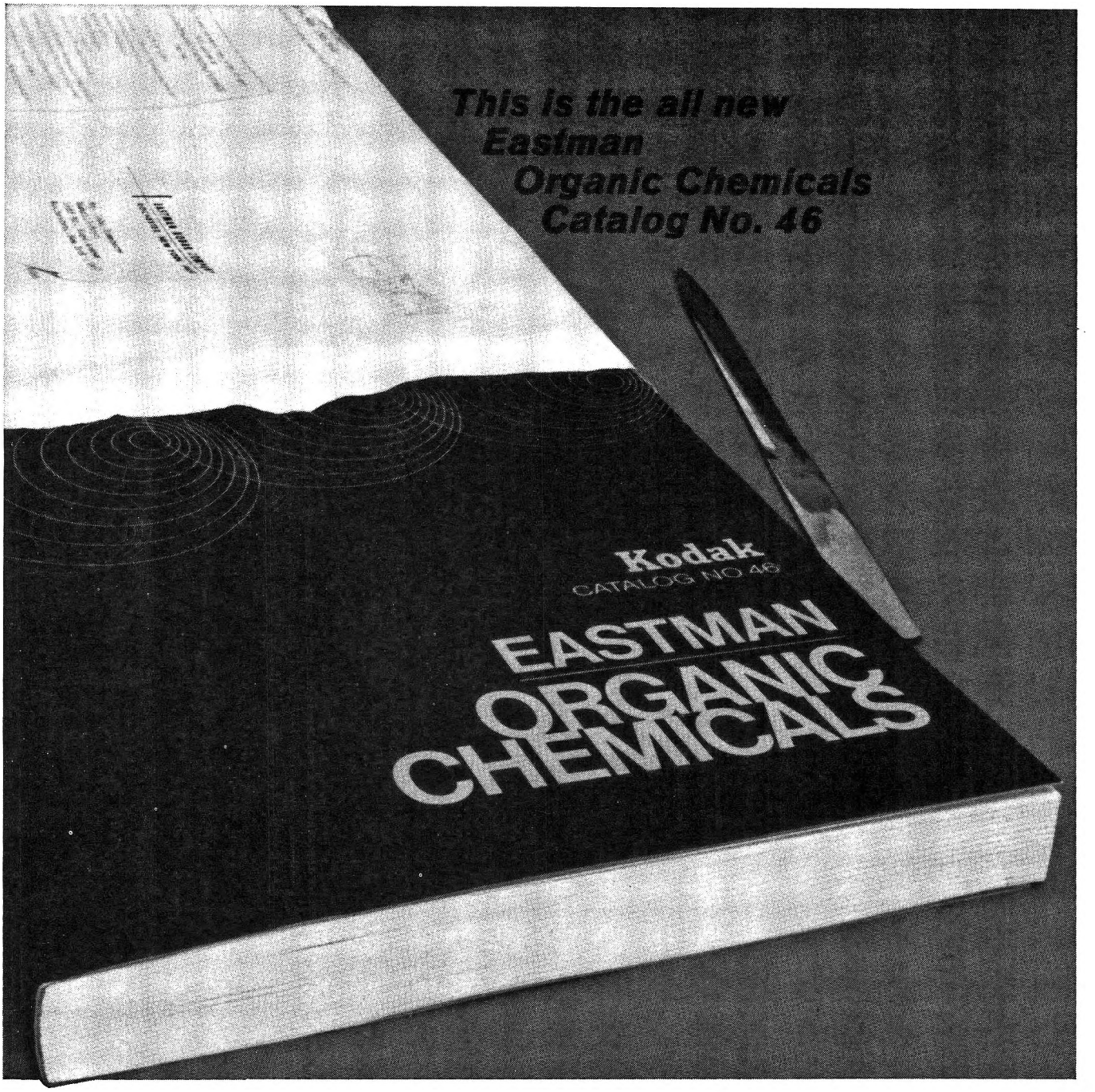
Anal. Calcd for $C_{15}H_{10}S$: C, 81.04; H, 4.54; S, 14.42. Found: C, 81.00; H, 4.49; S, 14.33.

Benz[*b*]indeno[2,1-*d*]thiophene-10-carboxylic Acid (13).—To a stirred, ice-bath cooled solution of 0.073 g (0.33 mmol) of **11** in 75 ml of dry ether under argon was added 0.31 ml of a 1.6 *M* solution of *n*-butyllithium *via* syringe. Upon addition the solution turned from red-orange to green. After stirring for 10 min, 15 g of CO_2 was dispersed into the reaction mixture. The color immediately reverted to yellow. After evaporation of solvent, the residue was dissolved in methylene chloride and this solution was shaken with a small amount of 3 *N* hydrochloric acid. Extraction with aqueous sodium carbonate, acidification, extraction with methylene chloride, and recrystallization from methylene chloride–hexane afforded 0.042 g of white benz[*b*]indeno[2,1-*d*]thiophene-10-carboxylic acid (**13**): mp 217–219°; ir (KBr) 3.20–3.60 (br), 3.75 (sh), 5.95, 7.15, 7.85, 8.35, 10.75, 13.40 μ; nmr ($DCCl_3$) δ 7.20–8.0 (m, 8 H), 4.90 (s, 1 H), acid proton apparently too broad to observe; mass spectrum m/e 266 (M^+, 100%), 267 ($M + 1^+$ 17.9%), 268 ($M + 2^+$, 7.4%); high resolution mass spectrum 266.040656 (observed), 266.040147 (calculated), 0.000509 (Δ).

X-Ray Solution of Adduct 12.—The stout, circular crystals of **12** displayed $2/m$ Laue symmetry in oscillation and Weissenberg photographs. Systematic extinction on $h0l$ (for $l = 2m + 1$) and $0k0$ (for $k = 2m + 1$) uniquely require the common monoclinic space group $P2/c$ (C_{2h}^5). The cell constants are $a = 11.800$ (5), $b = 5.87$ (1), $c = 8.270$ (6) Å, and $\beta = 104.35$ (5)°. Measured and calculated densities require $Z = 2$ on one-half molecule per asymmetric unit. A molecular inversion center may be excluded by the elemental analysis and a disordered model was anticipated. Complete data in hkl and hkl octants with $\theta \leq 30°$ were collected on a fully automated Hilger–Watts four-circle diffractometer using Zr-filtered Mo Kα radiation (0.7107 Å). A total of 701 reflections were judged observed after background and Lp corrections. The molecular outline was found quite readily by standard heavy-atom techniques. Full structural details may be obtained from the author (J. C.). Figure 1 is a computer-generated drawing of one of the molecules in a disordered pair. The final R is 0.110 for the 701 observed reflections.

Registry No.—**10**, 32120-91-5; **10** (sulfone), 32120-92-6; **12**, 23421-93-4; **13**, 32120-93-7.

Acknowledgments.—The authors are grateful to the Petroleum Research Fund, administered by the American Chemical Society (PRF No. 1152-G1), the Public Health Service (Grant No. GM-6689-02, National Institutes of Health), and the Atomic Energy Commission for their generous and continuing support of this work.



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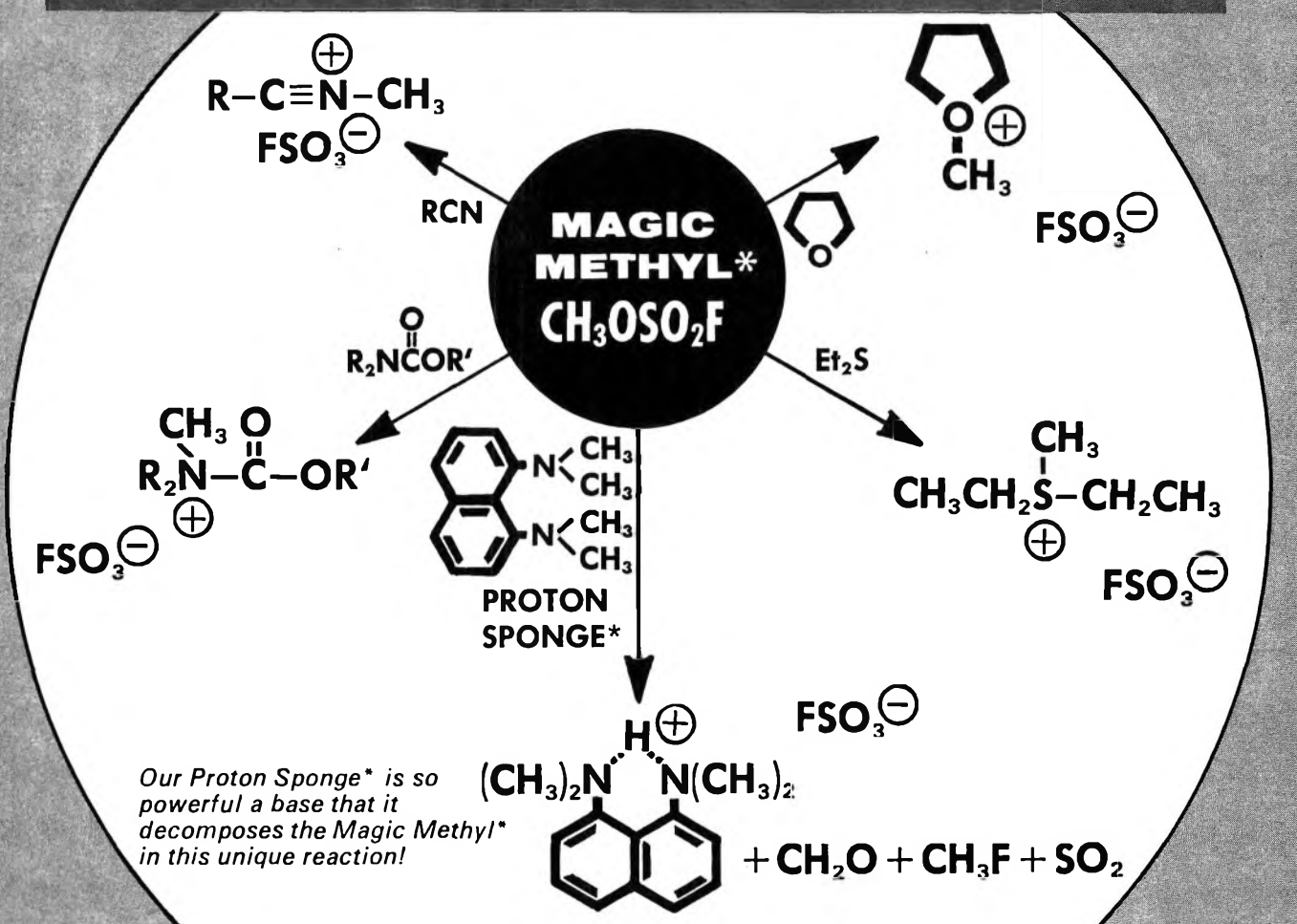

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1. M. G. Ahmed, R. W. Alder, G. H. James, M. L. Sinnott and M. C. Whiting, Chem. Comm., *1968*, 1533.
2. M. G. Ahmed and R. W. Alder, Chem. Comm., *1969*, 1389.
3. R. F. Borch, Chem. Comm., *1968*, 442.
4. R. W. Alder, private communication.
5. R. H. Mitchell and V. Boekelheide, Tetrahedron Letters, *1970*, 1197.

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